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## HARMFUL EFFECTS OF SHALLOW BREATHING WITH SPECIAL REFERENCE TO PNEUMONIA \*

JONATHAN MEAKINS, M D

MONTREAL

It has been demonstrated by Haldane, Meakins and Priestley<sup>1</sup> that abnormal shallowness of the respirations produces anoxemia. This is demonstrated by the occurrence of periodic breathing, cyanosis and other symptoms indicative of this condition.

The manner in which this abnormal type of breathing produces the anoxemia has also received considerable attention from them. Keith has demonstrated that the lungs do not expand after the manner of the bladder when external pressure is reduced, but like a Japanese fan. He has also pointed out that expansion of the lungs does not take place constantly and uniformly throughout. Therefore this type of breathing would of necessity exaggerate the uneven distribution of air to the alveoli.

They also found that the expired air and the alveolar air in cases exhibiting this type of respiration contained a large percentage of oxygen, which rendered it difficult to reconcile this condition with a pronounced anoxemia.

The circulation of blood through the different parts of the lungs is fairly uniform. As a consequence of the irregular expansion of the lungs, some part of the blood would be oxygenated well in the well ventilated parts, while some blood would be oxygenated poorly in the poorly ventilated parts, with the result that the arterial blood going to the heart would be a mixture of these two bloods, and depending on the shallowness of the breathing, the mixed arterial blood would obtain a greater or less amount of oxygen.

Reference to the dissociation curves of oxygen and carbon dioxide furnishes additional evidence as to how such a condition of anoxemia with high oxygen in the mixed alveolar air may occur. It is possible for the diminished removal of carbon dioxide from the poorly ventilated parts of the lungs to be compensated for by increased removal of

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\* Read before the Association for the Advancement of Clinical Investigation, Atlantic City, June 14, 1919.

1 Haldane, Meakins and Priestley. J. Physiol. 52:444 (May) 1919.

carbon dioxide by the well ventilated parts. Thus the carbon dioxide tension of the mixed arterial blood remains at a normal level. But in regard to the oxygen, it is totally different. "In the badly ventilated parts of the lung the volume of blood flowing per minute will be greater in relation to the amount of fresh air entering these parts than in the well ventilated regions. Hence, the blood will take up more of the oxygen and the percentage of oxygen in the relatively stagnant alveolar air of the badly ventilated parts will fall below the average. The dissociation curve of blood for oxygen is totally different from the carbon dioxide curve, and as the oxygen in the stagnant air falls, the percentage saturation of the blood passing through these alveoli must also fall greatly. But for oxygen pressures above about 88 mm Hg the curve is very flat. Hence, any increase of ventilation beyond the amount sufficient to keep the alveolar carbon dioxide at this level is quite unable to add appreciably to the amount of oxygen taken up by the blood. Thus it follows that in the well ventilated parts of the lungs first the increased ventilation is incapable of yielding an excess of oxygen to the blood sufficient to compensate for the lack of oxygen in the blood from the badly ventilated parts, and second, since more than the average amount of fresh air is passing through these alveoli, while no more than the normal amount of oxygen is being absorbed by the blood, the air expired from these well ventilated alveoli must be abnormally rich in oxygen. Thus the average composition of the alveolar air may remain constant as regards percentage of oxygen, as is normally the case, or, when the breathing is abnormally shallow, the oxygen content of the average alveolar air may rise above the normal level even though at the same time the arterial blood is inadequately supplied with oxygen."

The same authors have further pointed out that one of the respiratory responses to anoxemia is the occurrence of frequent and correspondingly shallow breathing<sup>2</sup>. Thus under certain circumstances it is quite conceivable that a vicious circle might be established.

These observations on shallow breathing resulted from an investigation of certain cases of "irritable heart" and "suffocative gas poisoning." But there are other cases of great clinical importance in which this same condition is found. The most important is pneumonia. It is a well known clinical observation that the severity of the symptoms in a case of pneumonia is not necessarily dependent on the degree of pulmonary involvement. A much more valuable indication as to the prognosis of the disease is the respiratory rate. It has been observed that as the respiratory rate increases the patient's condition becomes

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<sup>2</sup> Haldane, Meakins and Priestly. *J. Physiol.* 52: 420 (May) 1919.

more grave The point at which alarming symptoms develop varies in different individuals But, as a rule, in adults when the respiratory rate persists above 50 per minute cyanosis begins to develop This is a definite sign of pronounced anoxemia

The harmful effect of persistent anoxemia on the cardiovascular system is well recognized Of the fact that the cyanosis in cases of pneumonia is due to cardiovascular failure there is no definite proof Careful observation, however, will reveal the fact that the cardiovascular collapse is a sequel of the anoxemia

If the respiratory rate continues with sufficient rapidity and shallowness to produce persistent cyanosis, the cardiovascular system begins to show signs of failure, such as pronounced increase of pulse rate, gradual lowering of blood pressure with eventual collapse, the patient showing the "gray cyanosis" and other symptoms of "shock"

A number of cases of pneumonia have been investigated in order to determine the quantity and quality of the expired air For obvious reasons it was impossible to obtain the alveolar air in such cases It was found that as the respiratory rate increased, there was a gradual decrease in the volume per respiration, but the total ventilation per minute showed a conspicuous increase

On referring to Table 1 these points will be observed It will be noted also that, although the total volume per minute of expired air gradually increased, there is a very conspicuous diminution in the ratio between the volume of each respiration and the theoretical dead space This latter we may presume remains fairly constant in each individual case Therefore, the point may be reached where the alveolar air, expired or inspired, amounts to a comparatively few cubic centimeters, being undoubtedly insufficient to carry on any adequate pulmonary ventilation, so that eventually cyanosis develops

The respiratory quotient becomes progressively higher, at times it may reach 1.2, but when the crisis occurs there is a rapid return to normal not only in regard to the respiratory quotient, but also in so far as the respiratory rate, respiratory volume and total ventilation per minute are concerned It is not probable that this is due to any conspicuous change in the damaged lung, as all means of ordinary examination go to indicate that several days must elapse before such change is appreciable Furthermore, it is common knowledge that practically one half of the lung area may be nonfunctionating (artificial or spontaneous complete pneumothorax) without producing, while at rest, any evident respiratory distress

There is another aspect of this question which must be considered, namely, the part played by the pulmonary circulation Until recently it was not known to what extent the pulmonary circulation was inter-

TABLE 1—QUANTITY AND QUALITY OF EXPIRED AIR IN PNEUMONIA

No	Day of Disease	Pulse Rate	Temperature	Cyanosis	Respiration per Minute	Volume per Respiration, Cc	Volume per Minute in liters	Expired Air			Barometric Pressure	Result	Remarks
								Oxygen, per Cent	Carbon Dioxid, per Cent	Respiratory Quotient			
1	2	100	103.6	0	38	310	11.78	18.14	2.16	0.83	758		Right lower lobe involved
	4	101	101.4	0	45	270	12.15	18.20	2.13	0.86	752		
	6	120	101.2	+	54	230	12.42	18.84	2.14	1.01	763		
	7	140	101.6	++	60	210	12.60	19.13	2.00	1.11	757	Died	
2	3	100	101.1	0	42	300	12.60	17.89	2.86	0.91	755		Right lower and middle lobes involved
	5	110	101.0	0	44	294	12.03	17.06	2.70	0.87	754		
	6	108	101.2	0	45	290	12.75	17.08	2.83	0.93	752		
	7	100	98.0	0	34	330	11.22	17.40	3.24	0.88	753		
	8	80	98.4	0	24	420	10.08	17.14	3.20	0.85	757		
	9	81	98.2	0	18	505	9.09	17.04	3.58	0.86	758		
	1	110	101.4	0	40	300	12.00	17.75	2.79	0.83	759		
	6	108	101.1	0	42	286	11.91	17.04	2.82	0.91	756		
	7	104	101.3	0	45	270	12.15	18.01	2.84	0.94	748		
3	8	110	101.4	+	52	240	12.48	18.56	2.36	0.98	755		Left upper lobe involved
	8	124	102.3	++	54	232	12.82	18.82	2.18	1.03	766		
	9	130	103.2	+++	64	188	12.03	19.01	2.10	1.00	762		
	9	116	101.0	+++	66	160	10.36	19.30	1.96	1.23	761	Died	
	1	120	101.2	+	54	230	11.88	18.64	2.32	0.99	740		
	5	132	101.1	++	52	225	11.70	18.50	2.38	0.95	748		
	6	120	101.2	+	48	230	11.40	18.11	2.45	0.94	746		
	7	110	100.0	0	40	260	10.40	17.95	2.87	0.94	754		
	8	100	98.0	0	28	350	9.80	17.33	3.06	0.81	760		
4	10	80	97.4	0	18	510	9.18	17.01	3.16	0.85	762	Ortals Cured	

ferred with in pneumonia Gross<sup>3</sup> demonstrated that in pneumonia varying degrees of vascular obliteration may occur depending upon the stage of pulmonary consolidation In the stage of red hepatization there is a moderate preservation of the circulation, but there exist unusual clear spaces with poor injection, and even the injected vessels are somewhat narrowed and compressed In gray hepatization there is a general lack of injection, only several large branches moderately compressed may appear These injected branches end abruptly and the whole area of gray hepatization presents a striking anemic condition

It must be assumed that a certain volume of blood passes through the damaged lung area without being ventilated properly But it is not warranted to suppose that this nonventilated blood is sufficient in amount to reduce appreciably the oxygen content of the mixed blood entering the left side of the heart

This conclusion seems justified, therefore, that the anoxemia occurring in acute lobar pneumonia is the result of the rapid and shallow breathing typical of this condition

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3 Gross Canad M A J 9 632 (July) 1919

# CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

## LII STUDIES ON GASTRIC ULCER<sup>\*</sup>

A C IVY, PH D

CHICAGO

The studies on gastric ulcer as presented here are the first of a series of studies on the pathologic physiology of the stomach and duodenum in the condition of ulcer of these parts of the gastrointestinal tract

### I THE OCCURENCE OF ULCER AND OTHER PATHOLOGIC LESIONS IN THE STOMACH AND THE DUODENUM OF THE DOG AS JUDGED FROM ONE THOUSAND NECROPSIES

In a series of studies to be made on a pathologic physiologic condition it is obviously essential to make a study of the frequency of the occurrence of that condition in the animal used. A large amount of work has been done on gastric ulcer in which the dog has been the chief experimental animal. There are only two reports in the literature concerning the frequency of the occurrence of ulcer in the dog. Turck<sup>1</sup> reports a series of necropsies on 189 healthy and 82 diseased dogs in which the findings of "peptic ulcer" were absolutely negative. Other pathologic lesions, if they occurred, are not reported. Mann<sup>2</sup> reports a series of more than two hundred normal dogs and cats in which no "lesion of the gastric mucosa was found at necropsy." From the findings of these two observers one might conclude that the occurrence of lesions of the gastric mucous membrane of the dog are very rare. Since the data offered in the literature is meager, it was considered important to ascertain more completely the occurrence of lesions of the gastric mucous membrane in the dog.

### METHODS

The stomach and duodenum of healthy, diseased and experimental dogs was removed immediately after death and placed in cold running water where they were examined immediately, or always within one hour after removal. Quite a number of stomachs were examined a

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<sup>\*</sup>From the Hull Physiological Laboratory of the University of Chicago

1 Turck, F B J A M A 67 1784 (Dec 9) 1916

2 Mann F C J Exper M 23 203 (Feb) 1916

longer period after death than one hour, but observations on these were not recorded because of the possibility that any lesion present might be the effect of autodigestion

The lesions observed were classified as follows (1) Petechial hemorrhage, applied to the condition in which the red blood corpuscles are abundantly packed in the tissues of the mucosa and lie in the mucosa adjacent to the lumen, (2) superficial hemorrhagic erosion, applied to the condition in which there is an evident petechial hemorrhage accompanied by a superficial erosion of the cells of the mucous membrane, (3) acute ulcer, applied to the condition in which there is a well defined break in the continuity of the mucous membrane, (4) chronic ulcer, applied to the condition in which the edges of the ulcer are raised, undermined and thickened, and the base of the ulcer indurated, (5) diffuse inflammation, applied to the condition generally referred to as gastritis in which there occurs a swelling and hyperemia of the mucous membrane together with the production of a viscid adhesive mucus exudate and in acute cases with the occurrence of petechial hemorrhages and superficial erosions, (6) and tumors involving the mucosa I agree with Bolton<sup>3</sup> that it is neither useful nor correct to call a superficial hemorrhagic erosion an ulcer

### RESULTS

Table 1 shows the occurrence of pathologic lesions in the stomach and duodenum of healthy dogs that had been subjected to ether anesthesia for a period of two or three hours, while students used them for acute laboratory experimentation

TABLE 1—SHOWING LESIONS OF THE STOMACH AND DUODENUM (900 DOGS)

Lesions	Cardia		Fundus		Pylorus		Duodenum		Remarks
	No	%	No	%	No	%	No	%	
Petechial hemorrhages	11	1.2			26	2.9	13	1.4	
Superficial hemorrhagic erosions	1	0.09	1	0.09	23	2.5	6	0.6	Old emaciated dog
Acute ulcer					1	0.09			
Diffuse inflammation			4	0.44	4	0.44	23	2.5	Adenomatous polyps
Tumors					3	0.33			

The petechial hemorrhages and hemorrhagic erosions occurred chiefly in the last 2 inches of the pyloric portion of the stomach and in the first inch of the duodenum. In the case of the acute ulcer of the pyloric portion of the stomach there were two ulcers (2 by 1 mm), involving the entire thickness of the mucosa within one-half inch of the sphincter. The stomach was taken from an old emaciated



animal No apparent cause for the gastritis could be found Worms accompanied the enteritis in all except five animals, and may have been the cause in most cases <sup>4</sup>

TABLE 2—LESIONS OCCURRING IN THYROID PARATHYROIDECTOMIZED DOGS  
(TWENTY-FOUR DOGS)\*

Stomach	Stomach, No	Duodenum, No
Petechial hemorrhages	16	20
Superficial hemorrhagic erosions	13	15
Acute ulcer	1	3
Diffuse inflammation	9	18

\* One acute ulcer, 15 x 3 mm, almost perforated was found in the fundus Otherwise all the lesions in the stomach were confined to the pyloric portion

Table 2 shows the occurrence of ulcer and of lesions of the mucous membrane of the stomach and duodenum in animals dying of thyroid parathyroidectomy The paramount symptom that was manifested in the animals was depression, as reported by Carlson,<sup>5</sup> only 60 per cent of them showing tetany These animals lived from three to twenty days The severity of the intestinal findings was directly portional in most cases to the longevity of life following the operation

Eight out of forty dogs dying of distemper (snuffles) showed petechial hemorrhages and superficial hemorrhagic erosions of the pyloric and duodenal mucous membrane Acute gastritis and enteritis was present in every dog in this series Hypoacidity is a constant occurrence in these animals I have seen several cases in which raw meat would pass through the gastro-intestinal tract of a dog sick with distemper without being changed in color Diarrhea is also present in practically every case, as is anorexia and emaciation

In ten dogs dying of shock and symptoms of raised intracranial pressure following cerebral ablations, every one showed petechial hemorrhages and superficial erosions of the fundic and pyloric mucous membrane In four of these dogs the stomach was acutely dilated No free acid was present in the stomach of these animals

Out of twenty dogs that had been injected intravenously with ether twenty-four hours previous to death, five showed petechial hemorrhages and superficial erosions of the fundic and pyloric mucous membrane

Superficial hemorrhagic erosions occur frequently in dogs dying of experimental diabetes

A deeply eroded and indurated ulcer (4 by 6 mm), typically chronic, was found in the first quarter of an inch of the duodenum

<sup>4</sup> Food was present in the stomachs of about one half of the animals The lesions had no relation to the presence of food, however

<sup>5</sup> Carlson, A J Am J Physiol 30 1912

in a cachectic dog whose pancreatic ducts had been ligated five months previously and who had been kept on a diet of bread and milk. Hypoacidity was present in this dog. The dog died of acute stomatitis accompanied by rapid emaciation. The stomach and duodenum of twenty-four dogs, in which the pancreatic ducts had been ligated, were examined without finding ulcer. Four of these animals showed superficial erosions. In these dogs emaciation was marked and they died of distemper. The other animals were killed in other experiments, no lesions being present. With the exception of six of these animals, the pancreas was from macroscopic appearance atrophic and fibrotic. Jona<sup>6</sup> reports the presence of ulcers in the duodenum and small intestine following ligation of one pancreatic duct. From his picture and his description, I am led to believe that what he called ulcers were nothing more than Peyer's patches, which occur in the duodenum of the dog, made more conspicuous by emaciation and postmortem digestion. These patches are easily mistaken for ulcers, if a microscopic study is not made.

My observations on suprarenalectomized animals partly confirm those of Mann<sup>2</sup>. In forty suprarenalectomized dogs I have only seen one acute ulcer and twenty instances of petechial hemorrhage and hemorrhagic erosion of the gastric and duodenal mucous membrane, which is less frequent than reported by Mann.

Dogs dying immediately after section of the vagi and splanchnics not infrequently show petechial hemorrhages of the pyloric and duodenal mucous membrane. But in ten dogs that died or were killed from one week to four months following double vagotomy and splanchnotomy with extirpation of the celiac plexus, no gastric or duodenal lesions were found. Durante<sup>7</sup> reports that he observed lesions that were similar to acute and chronic ulcers in man. He does not state how long the ulcers were present and only states that such animals survive a short time. Most of my animals lived indefinitely and the nerve sections were verified at necropsy. Such animals become cachectic, however, and have to be cared for rather carefully for some time in order to keep them in a normal state of health.<sup>8</sup>

In a personal communication from Dr. S. A. Mathews, I was told that in Eck fistula dogs, which are kept alive for a long period on a diet of bread and milk and which are emaciated and cachectic, chronic ulcers of the stomach are frequently found.

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6 Jona, J. L. *M. J. Australia* **1** 316 (April 19) 1919.

7 Durante, L. *Surg., Gyn., Obst.* **22**:399 (April) 1916.

8 In an emaciated dog with gastrostomy and both splanchnics cut, Dr. A. B. Luckhardt found a chronic ulcer about one inch from the gastrostomy. The ulcer was about to perforate.

The three tumor formations found were adenomatous polyps which were confined in each case to the mucosa of the pyloric portion of the stomach

No scars were found in the stomach or duodenal mucous membrane These were looked for as probable evidence of healed acute ulcers Such scars are reported to occur frequently in man

#### SUMMARY AND DISCUSSION

It is apparent from the results of this study that chronic ulcer of the stomach and duodenum in healthy dogs and even diseased dogs, if it occurs at all, is very rare In diseased and cachectic experimental animals only two marked ulcerations were found one, very acute and almost perforating, the second, typically chronic On the other hand, petechial hemorrhages and superficial hemorrhagic erosions do occur in the gastric and duodenal mucosa of the healthy dog (I have seen them in the mucosa of the stomach even though the animal had not been subjected to ether anesthesia previously) These lesions, however, occur more frequently in experimental, diseased and cachectic animals

Comparing these observations with those reported to occur in man, it is seen that the dog is much less subject to gastric lesions than man According to Adam<sup>9</sup> "hemorrhages into the stomach wall are quite common" in man, and Birch-Hirschfeld<sup>10</sup> reports that they are found in 50 per cent of cadavers Osler<sup>11</sup> states that hemorrhagic erosions are common Chronic ulcer occurs in man as often as from 2 to 4 per cent Why there is such a difference between man and dog is a matter open for speculation If gastric juice digestion was a basic factor, we would expect more ulcers in the dog than in man as the dog's acidity is on the average greater than man's The dog being an animal generally of higher resistance and less subject to dietary, toxic and nervous factors, which cause gastric disturbance of motor, secretory and circulatory activity, than man, we would expect to find fewer ulcers The dog not being so subject to focal infections and hemorrhagic erosions as man, the dog would be less likely to have an ulcer hematogenous in origin Also, the dog being less subject to nervous influences, which cause hypomotility and hyposecretion, there would be less chance to infect a point of lowered resistance, a petechial hemorrhage or erosion, by bacteria swallowed These observations

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<sup>9</sup> Adam J Principles of Pathology, Philadelphia, Lea & Febiger, 1911, 2 414

<sup>10</sup> Birch-Hirschfeld loc cit, Adam

<sup>11</sup> Osler W The Principles and Practice of Medicine, New York, D Appleton & Co 1916 pp 490 447, 480

suggest at least that there is some factor present in man causing the chronicity of the ulcer which is absent in the dog, also, that if chronic ulcer can be produced in the dog's stomach or duodenum, it can be produced in man by the same method

The fact that chronic gastric ulcer does not occur and that gastric carcinoma is not found in the dog is comparative evidence, I take it, in favor of Mayo Robson's<sup>12</sup> theory of the etiology of carcinoma of the stomach in man. Mayo Robson suggested that gastric ulcer was the source of gastric carcinoma. Wilson and McCarthy<sup>13</sup> have presented evidence in support of this theory

## 2 THE EXPERIMENTAL PRODUCTION OF CHRONIC GASTRIC ULCER IN THE DOG

Petechial hemorrhages, superficial hemorrhagic erosions and acute ulcers have been produced experimentally in many ways: mechanically, chemically, by heat, drugs, toxins, peptones, serums, by section of the vagi and the splanchnics, by embolism and thrombosis, anemia, by feeding bacteria, by the intravenous injection of specific and non-specific bacteria, by abrasions, by lesions to the central nervous system, by removal of the suprarenals and parathyroids, and by many other methods. In other words, they are produced by anything that causes a local necrosis of the membrane by direct toxic or chemical action on the mucosal cells or by interfering or disturbing the normal condition of the capillaries of the mucosa. All biologic methods of producing the hemorrhages seem to point toward a marked susceptibility of the gastric and duodenal mucosal capillaries to injury by toxic and nervous influences.

Although acute ulcers have been produced in many ways, few investigators have claimed to have produced chronic ulcers of the gastric and duodenal mucosa. Bolton<sup>14</sup> and Friedman and Hamburger<sup>15</sup> were able to delay the healing of experimental acute ulcers by producing partial pyloric stenosis. Turk<sup>1</sup> reported that he was able to produce perforating ulcers of the duodenum and stomach by feeding *B. coli*. Durante,<sup>7</sup> by ligating and cutting the splanchnic nerves, reports the production of chronic ulcers. Rosenow<sup>16</sup> has reported the production of gastric and duodenal ulcers that "resemble those in man in location and tend to become chronic, to perforate and to cause hemorrhage" by the intravenous injection of alleged specific streptococci.

12 Robson, A. W. M. *Lancet* 2: 1547, 1904

13 Wilson, L., and McCarthy, W. C. *Am. J. M. Sc.* 846 (Dec.) 1909

14 Bolton. *Proc. Roy. Soc. Lond.* 82: 236, 1909

15 Friedman, J. C., and Hamburger, W. W. *J. A. M. A.* 62: 380 (Aug. 1) 1914

16 Rosenow, E. C. *J. Infect. Dis.* 19: 333 (Sept.) 1916

The chief views held at the present time concerning the etiology of chronic gastric ulcer are as follows (1) Infection of the mucous membrane through the blood by specific or nonspecific bacteria from a focal infection is the primary factor and the source of reinfection, (2) the digestive action of the gastric juice on mucosal cells that have had their normal resistance to acid peptic digestion diminished in some way, (3) a localized trophic disturbance is responsible for the chronicity of the ulcer, (4) the infection of the mucous membrane by swallowed bacteria

Most investigators in this field agree with Bolton<sup>17</sup> that chronic ulcer originates from an acute lesion and that most of the acute lesions heal rapidly

This study was undertaken as an attempt to throw more light on the experimental production of chronic ulcer in the dog

#### METHODS AND RESULTS

*Healing of Experimental Acute Ulcers*—The time required for the healing of acute ulcer produced by Roth's method (the injection sub-mucously of 10 cc of a 5 per cent silver nitrate solution) in the fundic and pyloric portions of the stomach and in the duodenum. Ulcers made in the mucous membrane of the fundic portion of the stomach healed in from nine to thirteen days, when ulcers were made in the pyloric portion of the stomach, healing required from twelve to eighteen days, if the dogs had the distemper, healing required from eighteen to twenty-two days. In the duodenum from sixteen to twenty-four days were required for the healing of the ulcer

This difference in the rate of healing is explained, I believe, by the anatomy and physiology of the different portions and the way in which ulcers of the mucosa heal. The manner of healing has been described in detail by Bolton<sup>14</sup> and Griffin and Vassale<sup>18</sup>

*Aseptic Embolism*—Injections of finely divided animal charcoal suspensions were made into the branches of the gastro-epiploic arteries with negative results. Suspensions of lead chromate and pigments were injected into branches of the gastro-epiploic arteries with resulting petechial hemorrhages and hemorrhagic erosions. Acute ulcers resulted in three of the animals injected with lead chromate. The results with lead chromate and pigments confirm the observations of Cohnheim<sup>19</sup> and Klebs and Welti<sup>20</sup>. Why the injection of animal charcoal gave negative results cannot be stated. The findings suggest

17 Bolton. *Ulcer of the Stomach*, London, 1913

18 Griffin and Vassale. *Ziegler's Beitr* 3 425

19 Cohnheim. *Lect on Gen Path* (New Sydenham Soc) 3 878, 1890

20 Klebs and Welti. *Handb d path Anat*, 1869

that effects produced by pigments and lead may be toxic and that an embolism produced by an inert, nontoxic substance, charcoal, will not result in hemorrhage or acute ulcer

*Ligation of Blood Supply*—Six to eight of the branches of the gastro-epiploic vessels supplying the pyloric portion of the stomach were ligated with negative results. This confirms the results of Littauer<sup>21</sup> who found that the blood supply to one third of the stomach could be cut off without producing deleterious effects and demonstrates a marked freedom of anastomosis

Silver nitrate ulcers were made in such an area to which the large blood vessels had been ligated with the result that they healed in normal time. The ulcers were made at the same time that the vessels were ligated

*Partial Pyloric Stenosis and Healing of the Ulcer*—The effect of partial pyloric stenosis on the rate of the healing of the ulcer was studied in eight dogs. In five the healing time of the ulcer was delayed from two to four weeks. No marked induration of the edges occurred in any case. The ulcers in the three dogs which did not manifest rapid loss of weight healed in normal time. To ascertain the condition of the ulcer, the dog was killed in some cases, in other cases operated on aseptically and the ulcer examined by direct inspection through an incision in the stomach wall. These findings confirm the observations of Bolton<sup>14</sup> and Friedman and Hamburger,<sup>15</sup> who report delayed healing in acute experimental ulcers accompanied by partial pyloric stenosis. Bolton reports delayed healing only, while Friedman reports a chronic ulcer at eight weeks after the production of the acute ulcer. Bolton accounts for the delayed healing as "due to necrosis of the base of the ulcer or excessive formation of sclerotic tissue therein, such conditions being the result of the low resistance which the connective tissues possess to digestion by gastric juice, or possibly in some cases to a secondary bacterial infection." Friedman and Hamburger account for the delayed healing by the prolonged action of the gastric juice and hyperperistalsis. Loss of weight and disturbed nutrition, which I observed in my animals and which is reported by both of the above investigators, although not emphasized, and bacterial infection of the acute ulcer must also be considered as possible factors in the delayed healing following partial pyloric stenosis

*Injections of Bacteria*—Injections of streptococci (one tube of a twenty-four-hours-old culture in dextrose ascites broth) were made into two or three branches of the gastro-epiploic arteries in a series of

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21 Littauer Virch Arch 195 No 2, 328

dogs with negative results. The dogs were killed from two to four weeks after the injection, so if any acute effects were produced, they did not persist nor leave scars. In two dogs killed twenty-four hours after the operation petechial hemorrhages were found. Perigastritis resulted in every case. Two strains of streptococci were used, one a *Streptococcus viridans* isolated from a tonsil, the other a *Streptococcus hemolyticus* from a case of septicemia. Dr. Clawson of the department of bacteriology, from whom the bacteria were obtained, stated that both were fatal for rabbits. The *S. viridans* when injected (three tubes of a twenty-four-hours-old culture of dextrose ascites broth) into dogs caused no symptoms, the *S. hemolyticus* when injected into dogs caused a rise in temperature, inactivity and loss of appetite of three days' duration. Although the bacteria were virulent enough to produce a dense fibrinous and fibrous perigastritis at the site of injection, no acute ulcers of the stomach resulted. These results suggest that either a markedly virulent or a specific bacterium is required to produce an acute ulcer of the stomach. I have injected streptococci beneath the skin and the mucosa of the stomach at the same time and in the same dog, in the former instance an abscess developed, while nothing resulted from the submucosal injection.

*Feeding Bacteria*—The effect of feeding bacteria to dogs in which an experimental abrasion of the pyloric and duodenal mucous membrane had been made was studied. The laceration was made under aseptic procedure through an incision in the anterior wall of the stomach by pinching and tearing the mucosa with a hemostat or extirpating it with the knife. Ten tubes of a twenty-four-hour-old culture of streptococcus were given daily by the stomach tube at a time when the stomach was empty. This was done in five healthy dogs with negative results, the laceration healing in from six to ten days and the extirpations in from twelve to fifteen days. In other words, Wilkensky and Geist's<sup>22</sup> observations were confirmed. The work was about to be given up when a sixth dog developed distemper after the operation and had recovered three weeks later. The dog was killed and a necropsy was made six weeks after the operation. A large hyperemic, edematous, inflamed ulcer (three-quarters of an inch in diameter) was found at the point of laceration. This dog had been fed *Streptococcus viridans*, which Dr. Clawson isolated from the deep tissues adjacent to the ulcer. The work was continued on two other distemper dogs and in two cachectic dogs with ligated pancreatic ducts. Six weeks after the production of the acute ulcer a necropsy was done on one of the distemper dogs. It revealed an ulcer with con-

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22 Wilkensky, A. O., and Geist, S. H. J. A. M. A. 66: 1382 (April 29), 1916.

gested and edematous edges with a thickened base. This dog had been fed *Streptococcus hemolyticus* which was isolated from the deep tissues about the edges of the ulcer by Rosenow's technic<sup>27</sup>. The second distemper dog which recovered from the distemper four weeks after the operation was killed four weeks later, or eight weeks after the production of the abrasion of the mucosa, and a healing ulcer (Fig 1)



Fig 1—Chronic ulcer (eight weeks) of the pyloric portion of the stomach produced experimentally



Fig 2—Chronic ulcer (ten weeks) of the duodenum produced experimentally

was found at the site of the abrasion. The edges were congested, edematous and markedly indurated. The cachectic ligated pancreatic duct dog showed at the site of the duodenal abrasion, which was made in this dog, an indurated ulcer with edematous edges (Fig 2) ten weeks after the production of the lesion. This dog continued to get more emaciated and weaker until it was killed.



The gastric juice and stomach contents of these dogs were examined at intervals for free acid. Free acid was not found at any time during the attack of distemper or during marked cachexia. This fact is well known to anyone who has worked with Pavlov pouch dogs sick with distemper or showing a disturbance of nutrition.

This study is being continued by a new method that will be more subject to experimental control.

#### DISCUSSION

The chronic ulcers produced in this study suggest that two other factors are necessary other than an abrasion with a trophic disturbance, infection via mouth or blood stream and acidity, namely, (1) a general lowered resistance, and (2) a temporary hypoacidity or achylia. The animals in which it was possible to delay healing of the acute lesion and to cause it to assume signs of chronicity by feeding streptococci were diseased and cachectic, and showed no free acid in their gastric

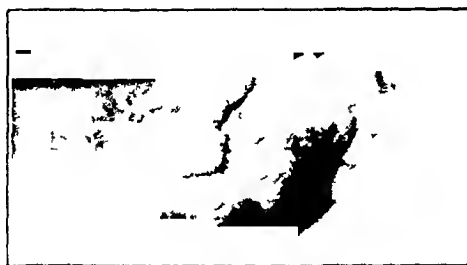


Fig 3—Ulcer found by Dr A B Luckhardt one inch from a gastrostomy opening in an emaciated dog with both splanchnics sectioned

juice or contents. It is to be recalled that it was observed in the first study on the occurrence of gastric and duodenal lesions that erosions are much more frequent in the experimental, diseased and cachectic animals. It is well known that diseased and cachectic animals show gastric juice that is deficient in free acidity and often entirely absent. This, of course, makes it possible for any bacteria swallowed or administered to become implanted in the abrasion or local area of hemorrhage or erosion, if present—free acid to the extent that occurs normally in the stomach being incompatible with life for most bacteria. Further, it should be pointed out that an infected lesion in a pathologic mucous membrane—for the mucosa of the stomach is pathologic when it is not secreting its normal gastric juice—is more likely to assume signs of chronicity and to become chronic than a lesion in a normal mucous membrane functioning normally. Therefore, given an abrasion of a pathologic gastric mucosa, a general lowered resistance by disease or disturbed nutrition accompanied by a hypoacidity, we have factors that

make it possible for bacteria swallowed or in the blood stream to become implanted in the abrasion and to produce local inflammation, induration, congestion and edema, and a chronic ulcer. Further, it is reasonable to believe, as observed and pointed out in one animal, that after the edges and base of the abrasion have become infected, inflamed and finally indurated—normal blood supply being diminished thereby—the general condition of the patient may improve or become normal, and yet have the ulcer remain chronic—because of the local diminution of blood supply and edema—and even to become more extensive because of mechanical irritation of coarse foods and tonic gastric activity associated with the action of acid pepsin on the devitalized tissue in the base and about the edges of the ulcer, or even a reinfection may occur during a period of hyposcretion following some digestive disturbance.

It is interesting to recall that acidity is generally considered the all-important factor in the chronicity of the ulcer, which is hardly tenable in light of my observations or those of Rosenow<sup>16</sup>. I recognize, however, that the chronic ulcer that I report might be considered by some to be different from the ordinary peptic ulcer seen clinically. My ulcers may be similar to those found in some cases of *achylia gastrica*, which some clinicians believe to have a different etiology than peptic ulcer, i. e., trophic.

These results explain the reports of many investigators who have ascribed some other cause to the delayed healing or chronicity. The results of Durante,<sup>7</sup> who produced ulcers chronic in character by section of the splanchnics, are in accord with this conception when the petechial hemorrhages, erosions, temporary hypoacidity and disturbed digestion and loss of weight, that often results along with the temporary lowered resistance from this operation, are taken into account. Durante reports that his animals lived only a short time, which supports my contention. Our double vagotomized and splanchnectomized dogs at this laboratory live indefinitely, but their feeding has to be carefully attended to for the first week or two—in a good state of health, which explains, I believe, why we found no ulcers in our series. Durante's ulcers were infected, as was shown by Rosenow. This conception is also in accord with the findings of Bolton<sup>14</sup> and Friedman and Hamburger,<sup>15</sup> who report that partial pyloric stenosis delays the healing of ulcer. The former investigator suggests that bacterial invasion may have been the cause. Both investigators report that such animals with partial pyloric stenosis vomit, lose weight and become cachectic. This also occurred in some of my dogs. Bolton reports that in some of his animals the gastric contents were neutral or alkaline, but Friedman and Hamburger state that "hyperacidity" resulted in

their animals. The effect of pyloric stenosis upon gastric secretion has not been thoroughly worked out, so this point cannot be settled. Turck's<sup>1</sup> results are in agreement with this conception. Turck produced ulcers by feeding *B. coli* in large amounts over long periods of time to animals that were confined and that manifested abnormal "systemic conditions" with "modified conditions of the alimentary tract." I was surprised to find that this conception is not contrary to Rosenow's observations. In looking over his protocols,<sup>16</sup> I find that the animals that showed chronic ulcers in his series had distemper or some general malaise as shown by anorexia and loss of weight. I do not accept the results of Rosenow as he interprets them with respect to chronic ulcer. Even if his specificity idea is accepted, that does not prove without question of a doubt, that this specific infection is the cause of the chronicity of the ulcer. A mycotic embolus is one of the factors causing acute gastric lesions, or the bacteria may infect an acute lesion otherwise produced. But it is agreed by most workers that acute ulcer in healthy animals heal rapidly no matter how produced. So it is very probable in the light of the results of other investigators and of the results obtained in this study that chronic gastric ulcer has its origin in an acute lesion of the mucous membrane which is infected by swallowed bacteria, or by bacteria from the blood stream, during a time at which the mucous membrane is pathologic—secreting none or but little free acid—and the general resistance is lowered by disease or disturbance of nutrition.

### 3 METHOD FOR MAKING A PYLORIC POUCH TO BE USED IN THE STUDY OF GASTRIC ULCER

Although several investigators have reported that they were able to produce ulcers of the chronic type, no one has seen a chronic gastric ulcer in the process of development. The method generally employed has been to produce an ulcer in the stomach by some means and then kill the animal some time later and ascertain the condition of the ulcer. Such a procedure is very unsatisfactory experimentally because of the presence of numerous uncontrollable factors. Hardt<sup>24</sup> and Dragstedt<sup>25</sup> approached nearer to the ideal experimental procedure when they studied ulcer in the Pawlow pouch. But in the Pawlow pouch one is working with a part of the stomach that seldom has ulcer, that heals rapidly, and that produces an acid secretion. The mucous membrane of the pyloric portion of the stomach, on the other hand, is the frequent site of ulcer, heals slower than the fundic mucous membrane.

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<sup>24</sup> Hardt, L. L. J. *Am J Physiol* 40 314 (April) 1916

<sup>25</sup> Dragstedt, L. R. *J A M A* 68 330 (Feb 3) 1917

and does not produce an acid secretion but a mucous secretion slightly alkaline in reaction. So it seems that the ideal experimental procedure, in which all factors might be controlled and chronic ulcer most likely to be produced under daily observation, would be to study the factors (acid, alkalies, irritation, motility, infection, with specific and non-specific bacteria, emaciation, etc.) that influence healing, positively or negatively, in a pouch of the pyloric portion of the stomach.

Hence the operative technic for making such a pyloric pouch has been worked out.

#### METHOD

Two methods are presented, one for making a pouch with nerves intact, the other for making a pouch with extrinsic nerve supply severed.

*With Nerve Supply of the Pouch Intact*—Approximately at a point on the anterior wall of the stomach where the fundic mucous membrane merges into the pyloric mucous membrane an incision one inch long is made through the wall into the lumen of the stomach (Fig 4, a). Through this incision the mucosa is everted and the original incision (a) is continued around the stomach, (b), cutting only the mucosa without cutting deeper than the submucosa (as in the Pawlow operation), thus dividing the mucosa into fundic and pyloric portions. The anterior and posterior edges of the fundic mucosa is then sewn together (Fig 5, c) with a continuous Lembert suture, as is also the anterior and posterior edges of the pyloric mucosa (d), thus forming a wall of the two mucous membranes, which divides the stomach into two compartments, the fundic and pyloric. The incision in the wall of the stomach (a) is then closed by a continuous suture. Next a posterior gastro-duodenostomy (e) is done connecting the fundic compartment with the duodenum. Then a pylorectomy (Fig 6, f) is done and the pyloric compartment is opened to the outside by a stab wound (g), the pyloric portion of the stomach being anchored to the abdominal wall by a series of interrupted sutures.

*With Extrinsic Nerve Supply Severed*—The pyloric portion of the stomach is separated from the rest of the stomach and from the duodenum by incisions "A" and "B" (Fig 7), care being taken not to interfere with the blood supply of the pyloric portion, which is to be the pouch. An end to side anastomosis (Fig 8, a') of the stomach to the duodenum is done and the cut end of the duodenum is closed (b'). Then the opening at the pyloric orifice (b) is closed. Next a large stab wound is made in the abdominal wall and the pouch is anchored in place. The reversal of the pouch so that "a" is brought to the outside instead of "b" makes a larger rosette and the mucosa of the pouch more accessible.

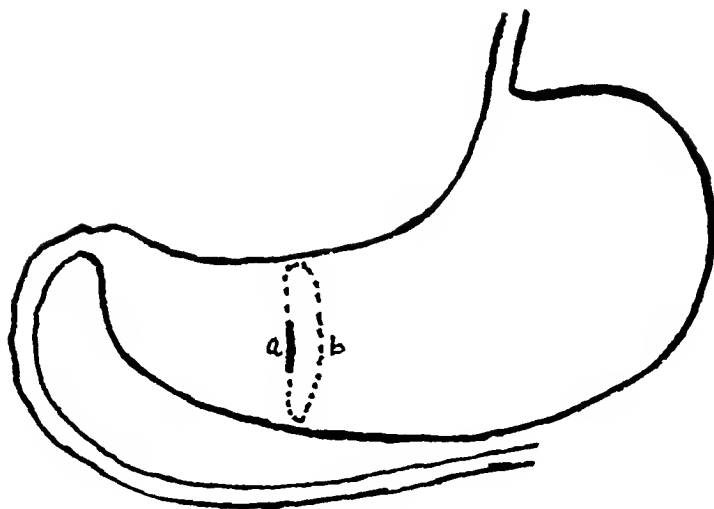


Figure 4

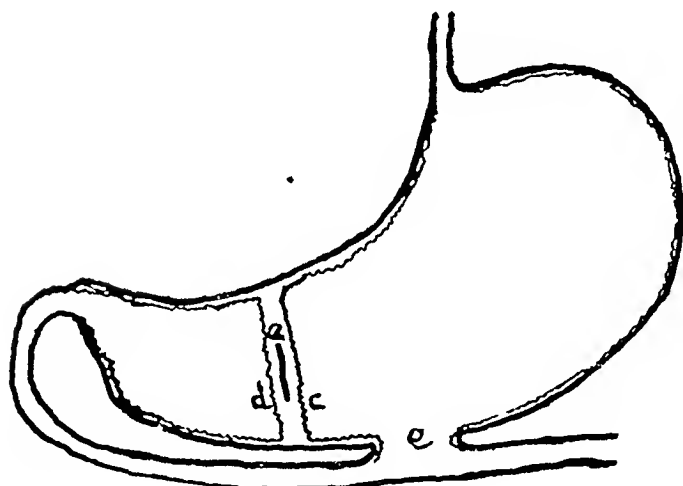


Figure 5

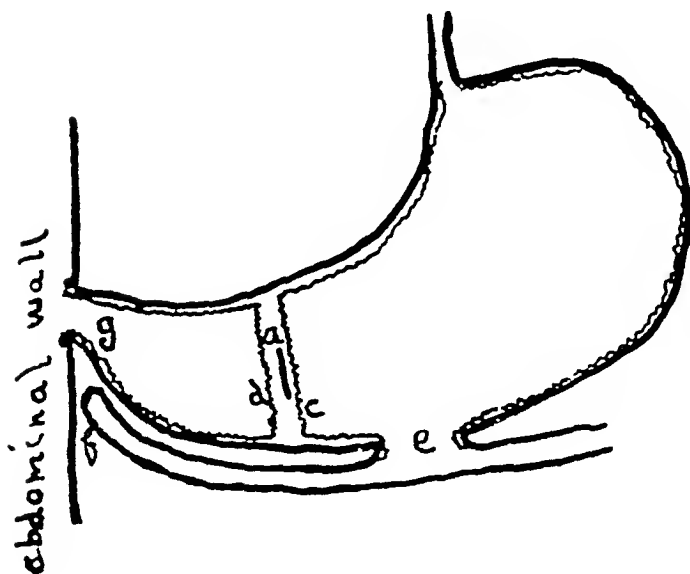


Figure 6

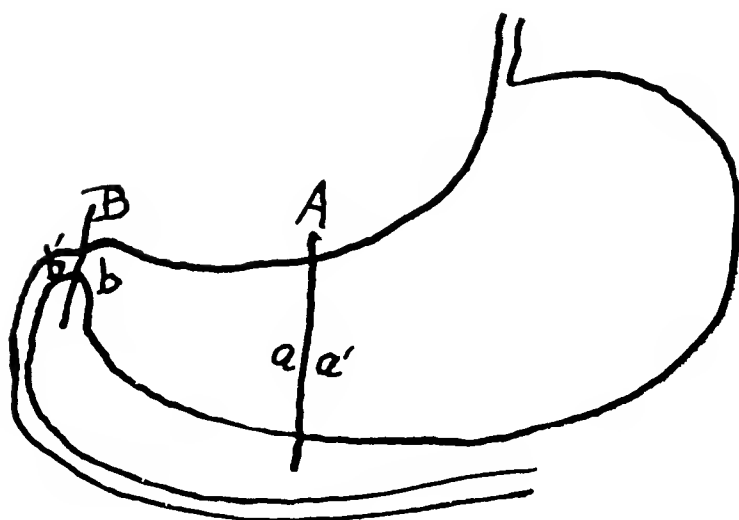


Figure 7

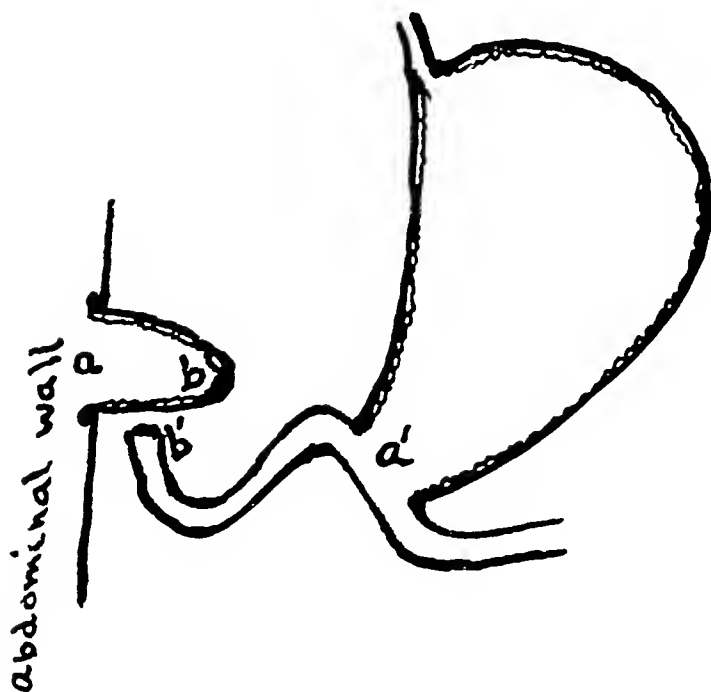


Figure 8

## RESULTS

Dogs operated on as described by these methods live indefinitely in a good state of health. Their feeding must be looked after carefully for the first week or two. Bones should not be fed until two or three months after the operation. They cause obstruction at the point of gastroduodenostomy.

The study of the experimental production of chronic ulcer and the factors influencing the healing of acute ulcers is being continued by this method.

#### 4 THE RELATION OF THE LOCATION OF THE ULCER TO CHANGES IN MOTILITY AND EMPTYING TIME OF THE STOMACH

All clinicians are generally agreed that in duodenal ulcer there is a retention of gastric contents and a hyperperistalsis of the stomach. The literature, however, is somewhat at variance concerning the motility of the stomach in ulcers of the pyloric portion of the stomach, unless a stenosis has been produced when the effects upon motility are practically identical with those of a duodenal ulcer. Dundon<sup>26</sup> studied the motility of the empty stomach in the condition of ulcer of the pyloric portion of the stomach and the duodenum. He concluded from his work that the motility of the empty stomach was greater in the condition of ulcer of the stomach and duodenum.

Desiring more complete and definite data on the relation of the location of the ulcer upon changes in motility and emptying time this study was undertaken.

## METHODS

The motility of the empty stomach was studied three to five weeks previous to the making of an acute ulcer. The criteria used were (1) the height of the contraction, (2) the frequency, (3) the length of the hunger and rest periods, (4) the type of the contractions, and (5) the postural and tonic activity of the stomach, the latter being determined by measuring the required amount of air necessary to be put into the balloon to raise the manometer level one inch.<sup>27</sup> This

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26 Dundon J. R. *Am J Physiol* 44 234 (Sept) 1917

27 The amount of air required is practically constant from day to day, never varying more than 5 cc. There is quite a variation between different dogs, varying from 15 to 40 cc. After section of the vagi the amount required is from 10 to 20 cc more than normal. This is only temporary, after from ten to twelve days the amount required becomes normal again. It is a question whether this is a true measure of the postural or tonic activity of the stomach. It points in that direction, however. The normal amount required is not influenced by ulcer of the stomach or duodenum. For a day or two after making the ulcer the amount required may be from 5 to 10 cc below normal, however.

method of putting a fixed amount of air in the balloon gave a constant base line from which one could comparatively judge more accurately the character of the motility. The size of the balloon, the time of starvation, and as far as possible, the diet were controlled. Bones were not allowed to be fed because they are sometimes found in the stomach twenty-four hours after feeding. The state of nutrition of the dogs was guarded carefully. Dogs with the mange, sniffles, or any other disease were discarded. Ulcers were made by injecting 15 c.c. of a 5 per cent silver nitrate solution beneath the mucosa. Ulcers were made in the anterior wall of the fundus in three dogs, in the anterior wall near the lesser curvature of the pyloric portion of the stomach from one-half to one inch proximal to the sphincter in five dogs and in the first inch of the duodenum in six dogs. Observations were made on the motility of the empty stomach for from three to seven weeks following the making of the ulcer.

Observations were also made on the emptying time of the stomach in ulcer of the fundic and pyloric portions of the stomach and the duodenum. A meal of 100 gm. of ground meat mixed with 50 c.c. of water was fed and its emptying time determined either by gastric fistula, emesis (morphin), and in some cases roentgenographically.

### RESULTS

Ulcer of the fundic portion of the stomach had no effect on the motility of the empty stomach, save a slight temporary inhibition for the first two or three days following the making of the ulcer. The same held true for the emptying time, no delay occurring. Healed ulcers were found at necropsy.

TABLE 3—MOTILITY OF THE STOMACH BEFORE AND AFTER ULCER OF THE DUODENUM, TWENTY-FOUR HOURS' STARVATION

Dog		Average Height of Contraction	Type	Average Length of Hunger Period	Average Length of Rest Period
IX	Before	5 cm	I	40 min	1½ hrs
	After	7 cm	I, II, III	2 hrs	1 hr
XII*	Before	Had to starve 80 hrs before contractions occurred			
	After	5.5 cm	I, II	30 min	1 hr
XVI	Before	7 cm	I, II	1¼ hrs	1¼ hrs
	After	9 cm	I, II, III	3 hrs	30 min
XXI	Before	4.5 cm	I	1¼ hrs	2 hrs
	After	9.5 cm	I, II, III	2¼ hrs	1¼ hrs
XXII	Before	5 cm	I	50 min	2½ hrs
	After	5 cm	I, II, III	3 hrs	1½ hrs
XXXIII	Before	5 cm	I	1 hr	3 hrs
	After	7 cm	I, II, III	3 hrs	1 hr

\* An old animal



Ulcer of the pyloric portion of the stomach caused in three out of five dogs an increase in the motility of the empty stomach. Here, too, a temporary inhibition of the motility for two or three days following the making of the ulcer occurred. The emptying time of the stomach was only interfered with in one of the dogs, in which there was a delay of two hours. In this dog at necropsy an extensive scar was found extending to the pyloric sphincter, but not involving it.

TABLE 4—SHOWING EMPTYING TIME OF THE STOMACH BEFORE AND AFTER ULCER OF THE DUODENUM

Dog	Normal Time of Emptying	Emptying Time after Ulcer, Duo	Time Delayed	Remarks
IX	3 hrs	5½ hrs	2½ hrs	On a full meal this dog often had food in the stomach 24 hours after feeding
XII	3½ hrs	5 hrs	1½ hrs	
XVI	3 hrs	5¼ hrs	2¼ hrs	
XXI	2¾ hrs	5½ hrs	2¾ hrs	
XXXII	4 hrs	9 hrs	5 hrs	
XXXIII	3¾ hrs	5 hrs	1¾ hrs	

Ulcer located in the first inch of the duodenum caused an increase in the motility of the empty stomach in all of the six dogs (Table 3, Figs 9, 10, 11 and 12). This increase was very marked in three of them. A delayed emptying time was observed (Table 4) in every animal. One animal showed a high grade retention to the degree that frequently food, that is on a full meal, was present in the stomach twenty-four hours after feeding. The hypermotility and retention only lasted from two to four weeks. On all these animals a necropsy was done and scars were found.

#### DISCUSSION

These results show that the clinical symptoms of chronic ulcer with respect to disturbed motility and emptying time of the stomach can practically be duplicated experimentally by an acute ulcer. The inhibition occurring for two or three days after making the ulcer is explained by the observations of Luckhardt<sup>28</sup> to the effect that gastritis inhibits motility, for a temporary gastritis is produced about the area of the injection of the silver nitrate. Why ulcer of the pyloric portion of the stomach and duodenum should disturb motility and ulcer of the fundic portion of the stomach is a question yet to be answered.

<sup>28</sup> Luckhardt loc. cit. Carlson, *The Control of Hunger in Health and Disease*, Chicago, 1916.

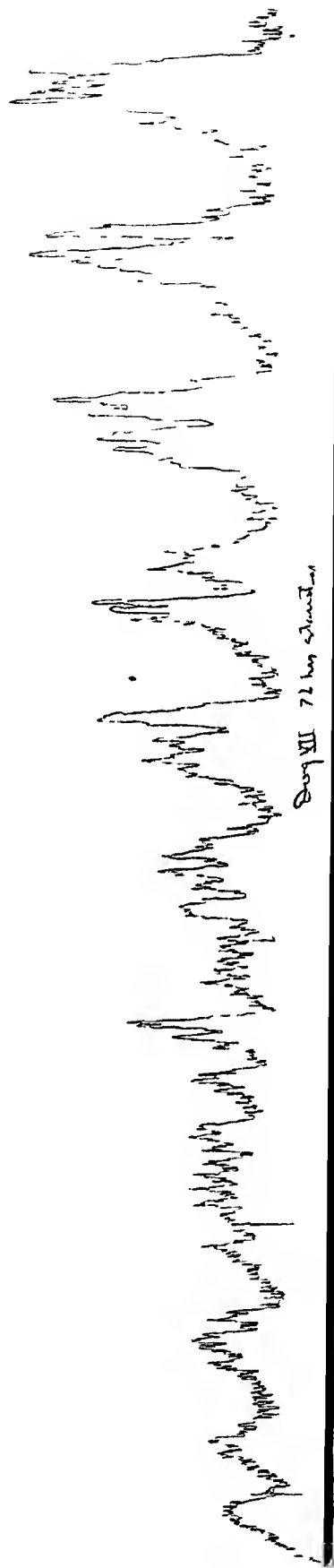


Fig 9—Contractions from an old dog (Dog 12, Tables 3 and 4) which had to be starved seventy-two hours before contractions occurred



Fig 10—Contractions from the same dog after forty-eight hours' starvation following a duodenal ulcer

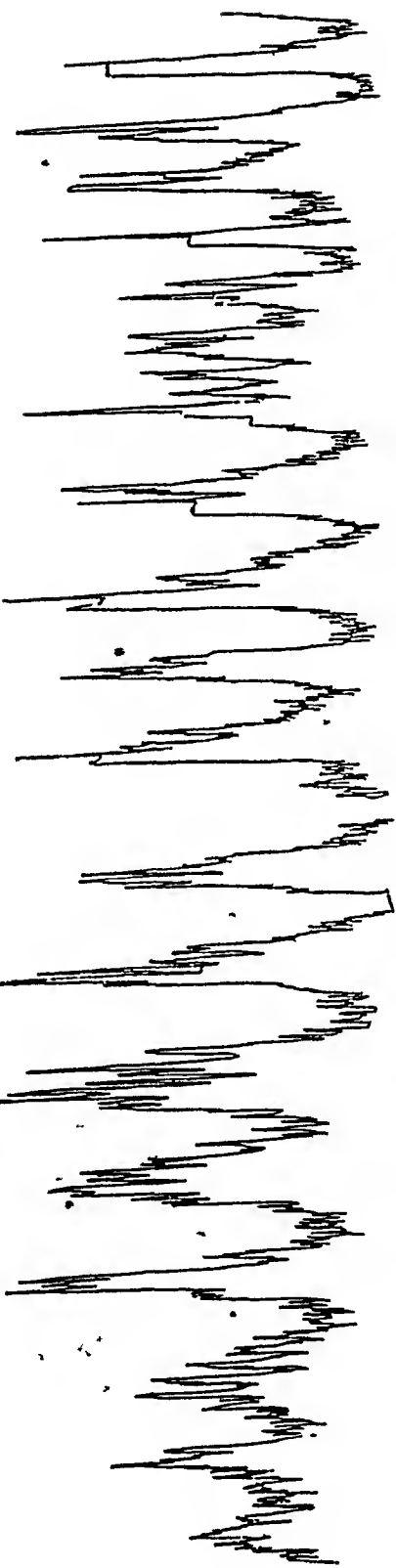


Fig 11 — Contractions from Dog 9 (Tables 3 and 4) before making the duodenal ulcer

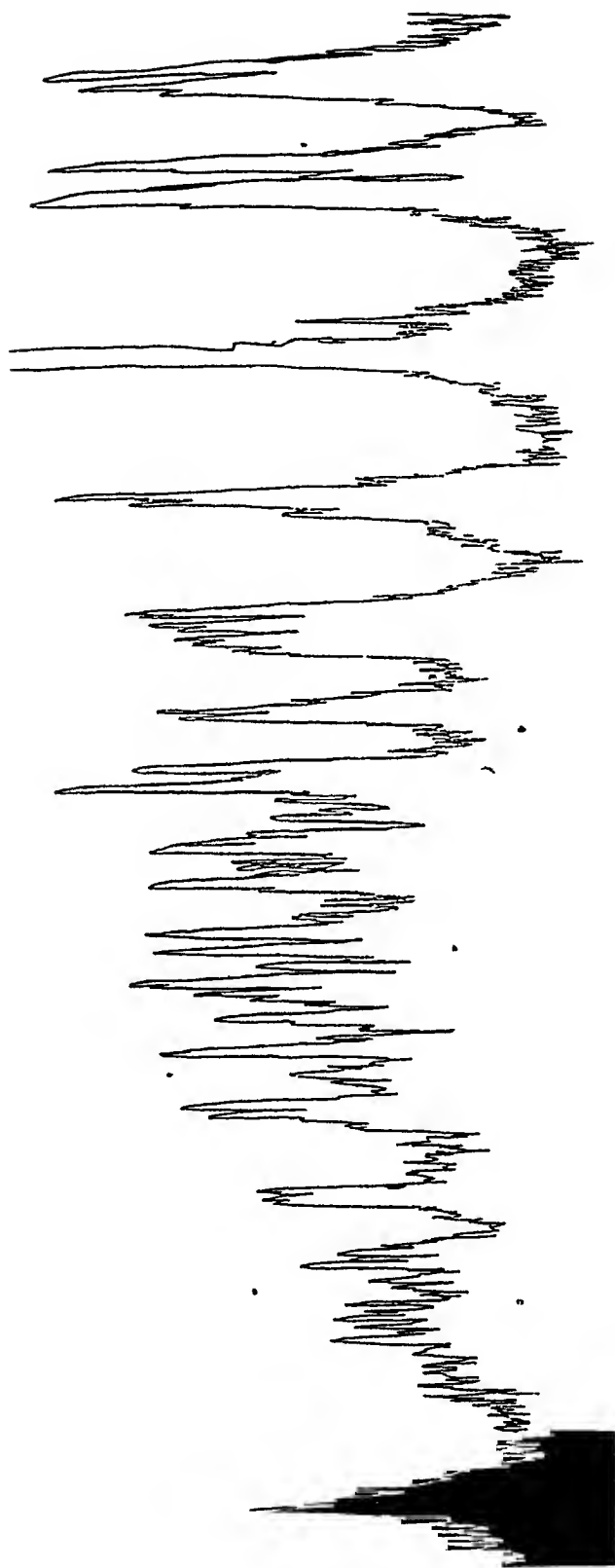


Fig 12 — Contractions from same dog after making the duodenal ulcer Dog was starved twenty-four hours in both cases

## 5 IS HYPERMOTILITY AND DELAYED EMPTYING OF THE STOMACH IN DUODENAL ULCER DUE TO AN INTRINSIC OR EXTRINSIC MECHANISM?

Hypermotility and delayed emptying of the stomach as a result of duodenal ulcer may be caused by either one or a combination of four mechanisms (1) to a long reflex to the cord and medulla, (2) to a short reflex to the celiac ganglion, (3) to a local intrinsic reflex, (4) or to an altered metabolic rate. Carlson<sup>29</sup> and Cannon<sup>30</sup> have shown that the isolated empty or full stomach, that is, with the extrinsic nerves sectioned, manifests normal movements. The movements of the isolated empty stomach are chiefly Type I, Types II and III, contractions seldom appearing. Brunemeier and Carlson<sup>31</sup> found that inhibition of contractions by acids, alkalies, water, milk, etc., occur in the isolated stomach, showing that it was possible to inhibit movements of the stomach via local or short nerve paths. Hicks and Vischer<sup>32</sup> showed that duodenal regurgitation when acid was in the stomach and that the characteristic movements by which this was accomplished occurred in the isolated stomach and duodenum. But the literature presents no evidence as to whether augmentation, or increased motility, can be brought about by local reflexes. On the other hand, the literature draws our attention to the importance of the extrinsic mechanism and uses the vagus nerve to explain all conditions of hypermotility, retention, pylorospasms, etc., without considering the possible importance of an intrinsic mechanism.

### METHODS

Both vagi and splanchnics were sectioned and the celiac plexus was extirpated. Records were made of the motility of the empty stomach, using the criteria mentioned in Study 3. An acute ulcer was made in the first inch of the duodenum and changes in motility were observed.

Observations were made on the emptying time of the stomach before and after the ulcer. A meal of 100 gm of ground meat mixed with 50 c c of water was fed.

### RESULTS

An increase in the motility of the isolated empty stomach occurred (Table 5) following the making of the acute ulcer in the duodenum (Figs 13, 14, 15 and 16). The degree of increase was not as great as that noticed when the extrinsic nerves were intact (Table 3). All

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29 Carlson, A. J. *Am J Physiol* **32**:369, 1913

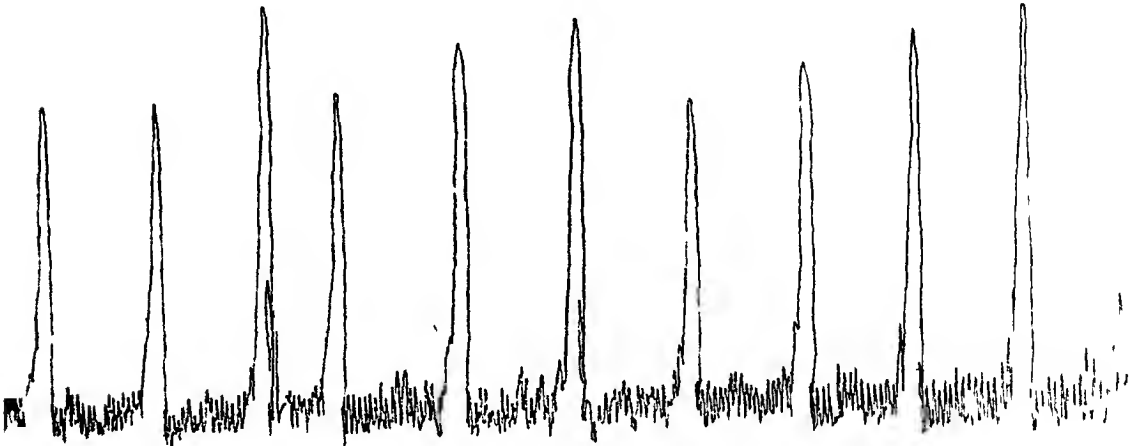
30 Cannon, W. B. *Am J Physiol* **36** 191, 1915

31 Brunemeier and Carlson. *Am J Physiol* **36** 191, 1915

32 Hicks and Vischer. *Am J Physiol* **39** 1, 1915

TABLE 5—MOTILITY OF THE STOMACH BEFORE AND AFTER ULCER OF THE DUODENUM IN DOGS WITH BOTH VAGI AND SPLANCHNICS SECTIONED AND CELIAC PLEXUS EXTIRPATED, TWENTY-FOUR HOURS' STARVATION

Dog		Average Height of Contraction	Type	Average Length of Hunger Period	Average Length of Rest Period
I	Before	6 cm	I	1 hr 40 min	2 hrs
	After	9 cm	I	3 hrs 20 min	2 hrs
I-A	Before	4 cm	I	1 hr	1 hr
	After	8 cm	I	2 hrs	45 min
XXXIII	Before	Contraction negligible on 24 hrs starvation			
	After	8 cm	I	3 hrs	30 min
XXI	Before	5 cm	I	30 min	1½ hrs
	After	7 cm	I	3½ hrs	20 min



Dog 33 - Vagi and splanchnics sectioned and celiac plexus extirpated. 48 hr starvation - no contractions on 24 hr etc return.

Fig 13—Contractions from Dog 33 (Tables 5 and 6) with both vagi and splanchnic sectioned and celiac plexus extirpated and starved twenty-four hours. Note type of contractions in the isolated stomach.

TABLE 6—SHOWING EMPTYING TIME OF THE STOMACH BEFORE AND AFTER ULCER OF THE DUODENUM IN DOGS WITH BOTH VAGI AND SPLANCHNICS SECTIONED AND CELIAC PLEXUS EXTIRPATED

Dog	Normal Time of Emptying of Isolated Stomach	Emptying Time after Ulcer of Duodenum	Time Delayed
I-A	3¼ hrs	4¾ hrs	1½ hrs
XXXIII	3¾ hrs	5 hrs	2¾ hrs
XXI	3 hrs	5 hrs	2 hrs

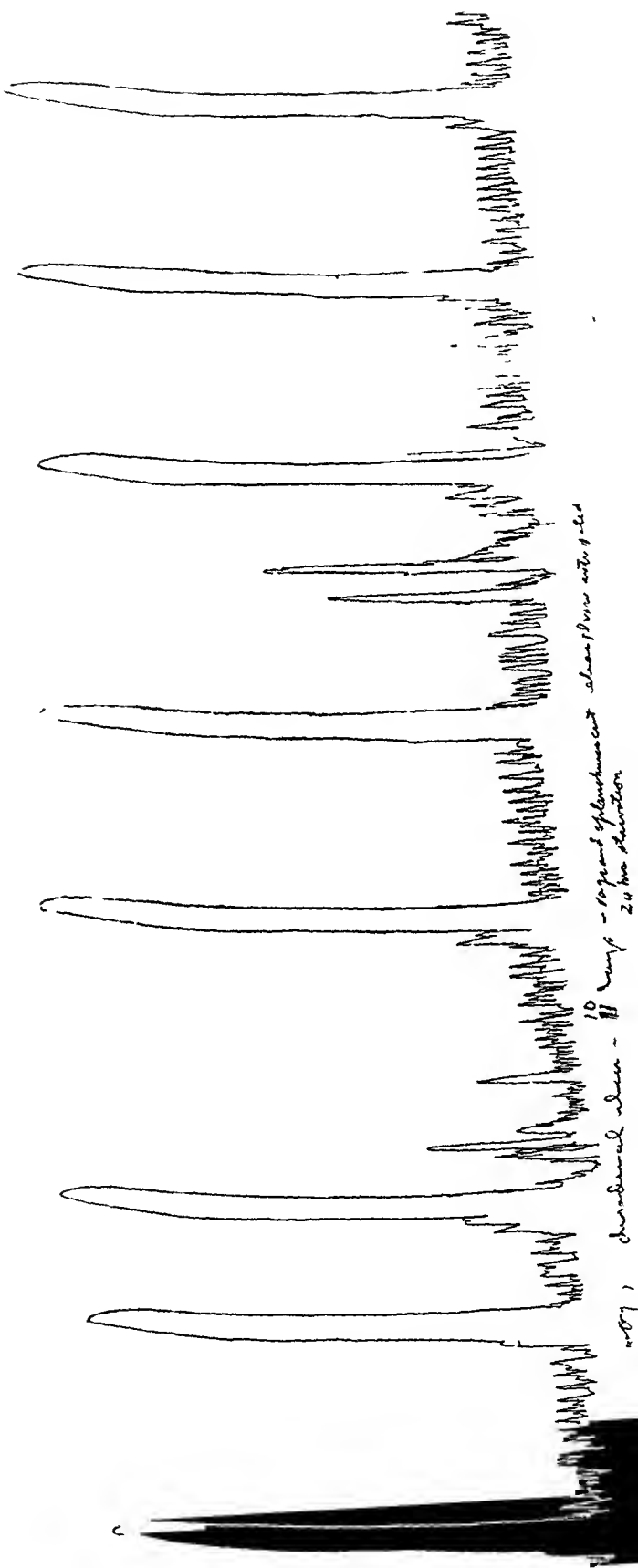


Fig 14—Contractions from the same dog after twenty-four hours' starvation with duodenal ulcer



Fig 15—Contractions from Dog 1 (Tables 5 and 6) with both vagi and splanchnics sectioned and celiac plexus extirpated and starved twenty-four hours

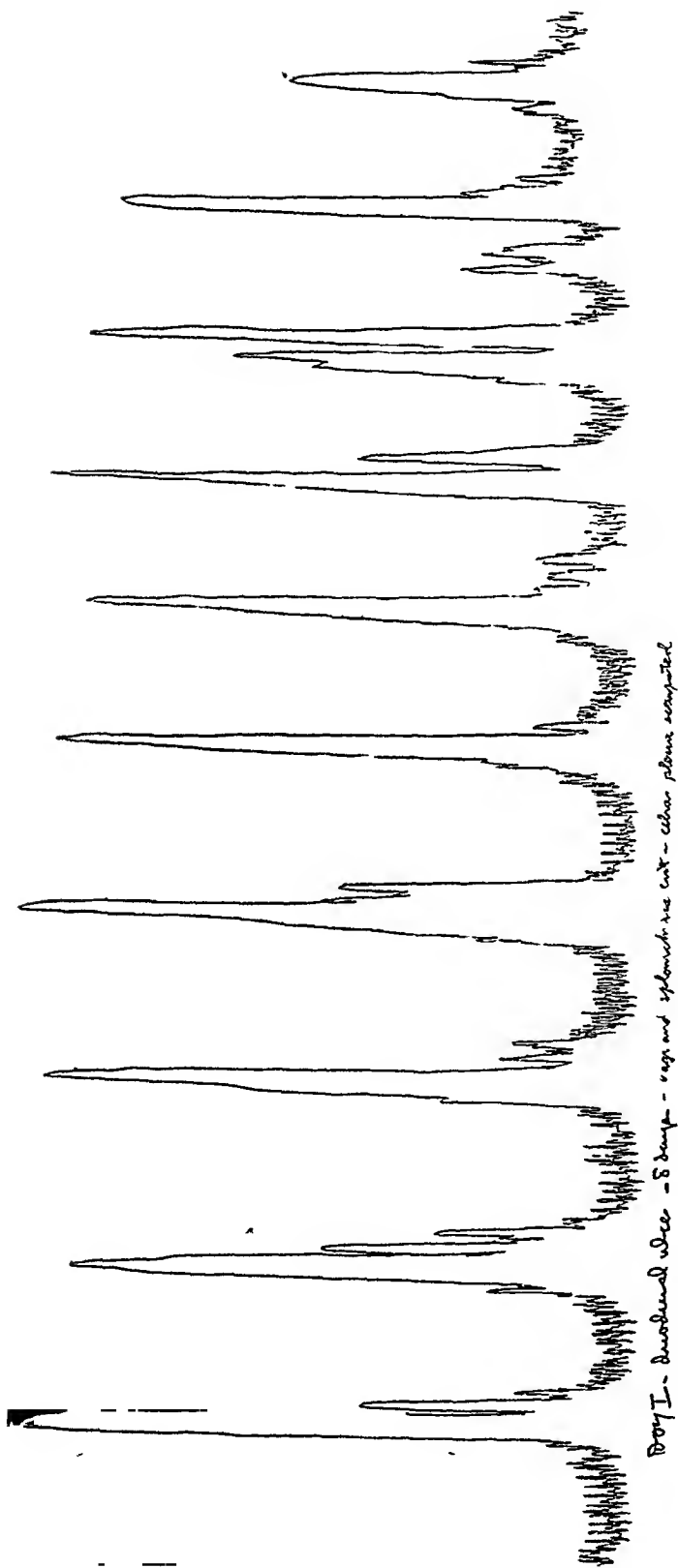


Fig 16—Contractions from the same dog after twenty-four hours' starvation with duodenal ulcer

contractions were Type I, showing that the prevalence of Types II and III in normal animals (Table 3) with duodenal ulcer was due to an extrinsic mechanism

The emptying of the stomach was delayed (Table 6), not so much as when the extrinsic nerves were intact (Table 4)

During the course of this study Brunemeier and Carlson's<sup>31</sup> observations on the inhibitory effect of alkalis and acids on the motility of the isolated stomach was repeated and confirmed

#### DISCUSSION

These results show that the fundamental cause of the gastric hypermotility and delayed emptying of the stomach in duodenal ulcer is intrinsic, and that it is enhanced by the presence of the extrinsic nervous mechanism, the rôle of the latter being to increase the frequency of the contractions occurring on gastric tone, or Types II and III

Although these results show that hypermotility and delayed emptying of the stomach in duodenal ulcer are due to intrinsic mechanism, they do not teach us the nature of the mechanism. There are two possibilities (1) an increased irritability of the intrinsic nervous reflex, and (2) an altered metabolic rate

#### ADDENDUM

Since writing this article my attention has been called to an article by Carman<sup>33</sup> in which he differentiates between extrinsic and intrinsic spasm by the use of atropin. He states that "intrinsic spasm plays an important part in the roentgenologic evidence of duodenal ulcers, and that in the absence of spasm no deformity of the bulb would be seen in many instances, and the case passed as negative." It is very interesting and important to note that my experimental results corroborate this clinical finding

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33 Carman, R. D. J. A. M. A. 66 1283 (April 22) 1916



# THE EFFECT OF ROENTGEN RAYS ON THE METABOLISM OF CANCER PATIENTS \*

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AND  
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The ever increasing scope of blood chemistry studies has enabled us to estimate quantitatively factors representing protein, fat, carbohydrate and salt metabolism and storage

Everyone is familiar with the cachexia of cancer sufferers, and the early stage at which it sometimes appears, making it practically a diagnostic symptom of malignancy With this in mind, our efforts have been directed toward the actual cause of the loss of weight, whether due to (1) deficient food intake, (2) absorption of toxins from secondary infection of the tumor, or (3) to some specific action of cancer cells that prevents storage and utilization of foodstuffs

Following radium and roentgen-ray treatments, many patients show marked improvement or are cured, and the question arises as to whether the roentgen ray produces any discernible change in the blood chemistry and how long such a change must exist to affect a general improved metabolism, and whether the effect of the roentgen ray is a general one or only a local destructive action on tumor cells

We, therefore, chose ten readily estimable factors for the study of the blood chemistry, and the complete studies were made immediately before roentgen ray exposure, one half an hour after, and on the next day, approximately twenty-four hours afterward The entire study is preliminary to, and in the nature of a report of the broader observations with which we are now engaged The following were estimated in mg per 100 c c of blood in each instance 1 Urea 2 Creatinin 3 Uric acid 4 Chlorids 5 Cholesterol 6 Fatty acids 7 Total fats 8 Sugar 9 Diastatic activity 10 Plasma and corpuscle percentage The cases selected for study were not taken at random as only those patients were selected who were practically free from renal disease, in order to obviate the matter of retentions Several control studies were made on normal people subjected to the same roentgen-ray exposure With another control group of cancer patients, we took 60 c c of blood at the same interval as in the roentgen-ray studies but without roentgen-ray exposure

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\* From the New York State Institute for the Study of Malignant Disease, Buffalo, N Y H R Gaylord, M D, Director

## UREA

The urea content of the blood has been much studied as to its source and utilization. It bears a close relation to the amino acids and its production probably depends on the activity of all the living

TABLE 1—UREA NITROGEN CONTENT OF BLOOD  
Mg per 100 c c

Number	Before Roentgen-Ray Exposure Per Cent.	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent
1	56	140	84
2	120	210	126
3	98	140	140
4	56	70	140
5	168	196	154
6	140	70	84
7	126	140	84
8	70	42	28
9	118	140	168
10	84	136	336
11	118	126	98
12	154	168	140
13	98	126	84
14	98	84	98
15	98	140	126
16	126	154	140
17	112	140	238
18	98	252	112
19	98	126	126
20	238	154	168
21	112	238	186
22	56	84	56
23	140	140	140
24	112	112	70
25	112	84	818
26	197	210	112
27	140	126	224
28	168	238	182
29	112	154	210
30	56	98	56
31	126	178	196
32	84	112	252
33	126	140	112
34	56	238	210
35	118	266	98
36	906	154	210
37	120	180	
38	168	182	
39	295	280	
40	84	98	
41	98	140	

cells rather than of any fixed group. With renal injury, either slight or severe urea is so consistently retained and piled up in the blood stream that a definite prognosis can be given such a case on the

amount of urea present. It is an excellent kidney function index, and can be used practically alone as such, if the protein intake is known. McLean and Mosenthal have worked out the index of urea excretion with precision and added much to our knowledge of its value in the prognosis and treatment of various renal diseases.

Its relation, however, if it has any special one, to malignancy has not yet been recorded, and the few observations we make at this time are entirely preliminary to our more complete studies of urea and the amino acids in relation to cancer. There is some question as to whether the rapidly growing tumor cells have a special activity as regards urea and amino acid chemistry, apparent early in the pre-cancerous condition and which would thereby aid in diagnosis and treatment at an earlier stage. Of the forty-one cases studied, eleven patients were improving, seven had had tumors removed and were improving, twelve were progressing and six were clinically well. Thirty-one cases showed increased urea, one half hour after roentgen-ray exposure, and of these, twenty still showed increased urea on the day following. Of the seven cases with urea decreased one-half hour after roentgen-ray exposure, five were progressive with no improvement, one was a healthy person and one had an improving epithelioma of the nose.

It can, therefore, be seen that there is nothing characteristic about the conduct of urea formation that would aid in early diagnosis without the simultaneous amino acid and protein intake studies. The increase in urea was at no time exceedingly high. It was only a relative increase. The reduction of body proteins into amino acids, and urea formation therefrom could account for the slight increases, and it is quite possible that the tumor cells, exposed to the roentgen rays, themselves furnish enough amino acids to account for the increase in urea in some of the cases. The increase one-half hour afterward in some cases, and not until the day following in others, can be accounted for partly by the variation of response of living tissue to the same stimulus. It is possible that the conversion of proteins to amino acids is accelerated in these exposed cases by ferments activated by the rays, in which case the exposure of any part of the body other than the tumor would have the same effect on the urea chemistry. As there is still some indecision as to whether there is actually the same result with diffuse exposure to roentgen rays we cannot at present make a definite statement. The urea determinations were made by the urease, aeration and titration method with control checks to insure their accuracy.

## CREATIN AND CREATININ

The study of the metabolism of creatin and creatinin in malignancy has been very limited, and it has only been in recent years that the definite relationship between the two has been made clear. Methods

TABLE 2—CREATININ CONTENT OF BLOOD  
Mg per 100 c c

Number	Before Roentgen Ray Exposure Per Cent	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent
1	0.66	0.571	0.09
2	0.26	0.63	0.5
3	0.8	0.62	0.7
4	0.83	0.67	
5	0.71	0.68	
6	0.43	0.58	0.5
7	0.52	0.55	0.35
8	0.58	0.39	0.45
9			
10	0.8	0.56	0.13
11	1.0	0.91	0.72
12	0.73	0.85	1.37
13	0.8	1.1	0.57
14	1.1	0.76	0.71
15	0.89	0.99	0.5
16	0.99	0.8	1.05
17	0.4	0.4	0.4
18			
19	0.714	0.714	1.01
20	0.83	1.142	1.25
21	0.909	2.22	0.5
22	0.909	0.52	0.26
23	0.8	1.25	0.71
24	0.909	0.909	0.606
25	0.9	0.44	0.54
26	0.59	0.67	0.72
27			
28	0.5	0.5	0.53
29	1.05	0.571	0.09
30	0.63	0.53	0.5
31	0.87	0.5	0.83
32	1.0	1.1	0.8
33	0.95	0.85	0.9
34	0.83	0.84	0.87
35	0.83	0.83	0.83
36	1.81	1.33	1.1
37	0.66	0.71	
38	1.2	1.2	
39			
40	0.81	0.85	
41	0.57	0.88	

for the determination of these factors in the blood can still be improved. In our work we used acetic acid precipitation of the blood and picric acid precipitation with parallel results but rather low readings. Although in all instances it was possible to recover

creatinin which we added to the blood, we are not satisfied that we have completely extracted the creatinin already present in the blood Meyer and Fine<sup>1</sup> have shown, that creatin is slowly changed to creatinin even in pure solution, and much more rapidly in autolyzing muscle tissue The increased creatinin in the blood in nephritis is due most probably to a retention rather than to an endogenous increase as it becomes much higher in the blood than in the muscle tissue itself, and there is practically no alteration in the creatinin content of either Marcelle Wahl<sup>2</sup> studied creatin in the urine of a variety of diseases, and among them some cases of cancer In cancer with no metastasis in the liver he found barely a trace of creatin, but, on the contrary, in cases of cancer with liver metastases the elimination of creatin was definitely high

R A Chisholm<sup>3</sup> reported a study of creatinin content of muscle in malignancy, but although there is a great deal of literature on the relation of creatin and creatinin to muscle activity, starvation, pregnancy, nephritis, etc, further studies have been much lacking in regard to this factor and its relation to cancer

Fifteen of our cases had an increased amount of creatinin in the blood one-half hour after roentgen-ray exposure, in twenty cases it decreased the day after, and in eight it was still increased on the day following when three cases showed no change in the amount of creatinin and eighteen cases were decreased one-half an hour after roentgen-ray exposure There were no renal cases and no creatinin content greater than would be expected in the normal person

We can find nothing characteristic of cancer in the variation of the creatinin content of the blood, and apparently there is no alteration of creatinin metabolism in this disease

#### URIC ACID

Uric acid was discovered in urinary calculi in 1776 by Schule, and in gouty tophi by Wallaston in 1797 In 1882, Salkowski introduced a method for the quantitative estimation of uric acid, and altogether, during the past century and a half, an enormous amount of research has been done on this subject not only on humans, but on the lower animals, including birds

About 1899, Emil Fischer classified uric acid as a definite chemical entity, and showed its relation to the purin nucleus and other bodies as hypoxanthin, xanthin, adenin, and guanin, all of whose structures

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1 Myers, V C, and Fine, M S J Biol Chem **21** 460 (June) 1915

2 Wahl, Marcelle Arch de med exper et d'anat path **28** No 2

3 Chisholm, R A Biochem J **4** 243, 1911

depend on slight changes around the purin nucleus Salmon, in 1880, discovered that purin bases exist in nuclein of cell nuclei, and that the products obtainable from nucleoproteins are varied and numerous

TABLE 3—URIC ACID CONTENT OF BLOOD  
Mg per 100 cc

Number	Before Roentgen Ray Exposure Per Cent	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent
1	2.9	4	4
2	3.2	2.42	4.1
3	3.75	2.66	3.15
4	3	2.85	3
5	1.29	1.26	0.93
6	2.5	2.85	3.92
7	4.4	3.9	4
8	2.66	3.33	3.8
9	4.46	2.94	1.1
10	3.8	3.6	3.6
11	3	3.3	4
12	2	2.35	1.33
13	1.9	2.85	2.9
14	2.58	1.87	1.75
15	2	1.14	2.5
16	2.5	2.5	2.6
17	3.63	3.07	3.8
18	1.74	3.125	3.85
19	1.89	1.89	3.63
20	2.17	1.85	1.81
21	2.8	3	2.5
22	2.2	2.5	1.9
23	1.81	3.3	1.81
24	3	3	1.3
25	5.3	4	4
26	5.5	6.25	3.57
27	5.5	5	4.54
28	2	1.3	4
29	2.02	2.5	5.5
30	2.85	3.07	5.71
31	2	2.5	2.5
32	3.33	3.65	3.2
33	1.29	1.93	1.28
34	2.34	3.63	3.63
35	1.81	2.27	3.22
36	1.8	2.7	1.15
37	2.71	0.857	
38	2	2.17	
39	3.28	3.57	
40	1.8	2	
41	2.3	2.1	

The normal range of uric acid in the human blood is from 0.5 to 1.5 mg per cent. It is rarely below 0.5 mg and commonly over 1 mg.

The sources of uric acid in the blood may be divided into 1 Exogenous or ingested 2 Endogenous or from body catabolism

The exogeneous source of uric acid is from foods containing purins and nucleoproteins, such as meat extractives, glandular tissue, peas, beans, etc. The purins ingested as free base or as nucleic acid are at least partially converted into uric acid which is the most highly oxidized member of the purin compounds. We still know very little of catalytic processes of purins in the body. Uric acid in the blood is excreted for the most part and very little is oxidized in the body. Its excretion is increased after ingestion of purins or any food that increases its concentration in the blood. Uric acid is a physiologic diuretic and its excretion depends chiefly on kidney cell activity so that it is being constantly excreted in varying amounts, but always with an effort at maintaining a constant concentration in the blood. If there is any kidney injury, such as occurs with varying degrees of nephritis, the threshold of excretion of uric acid is raised and the "constant concentration" of the uric acid in the blood is much higher than normal and may reach a level of from 6 to 8 mg per cent. This level may become very high with unrestricted purin diet, but, of course, in a true retention of uric acid there are the other signs and symptoms of renal insufficiency to aid in a diagnosis.

There is the gouty type in which there seems to be a selective retention of uric acid. Purin diet, in these cases, gives a very high blood uric acid which, however, is excreted on the administration of atophan and salicylates, until a normal level is reached. The high uric acid of renal insufficiency does not behave in this way, as medication acts only as an irritant to the already overworked cells and serves to cause a greater retention than before. In an actual nephritis, where the uric acid in the blood comes from both exogenous and endogenous sources, its concentration in the blood can be lowered effectively by restricting all purin foods. We can see what an important part the exogenous source of uric acid plays in keeping up the normal amount of uric acid in the blood. It is easily observed and controlled, and it is quite simple to eliminate this source of a high uricacidemia, in making a study of a case.

Endogenous uric acid has several sources, much more difficult to study than the exogenous variety. We are unable to tell exactly where the endogenous purin precursors of uric acid are, but we can say that the breaking down of body purins, such as the free hypoxanthin of muscle, and the breaking down of nucleoprotein from pus cells as in focal infection or leukocytosis, or from local necrosis in any parenchymatous tissue, form the chief sources of endogenous uric acid. Exercise, of course, increases the uric acid in the blood.

and it is well known that uric acid is increased in the leukemias where there are so many leukocytes constantly breaking down and undergoing digestion. Valuable information can be obtained as to the existence of focal infection by studying the uric acid in the blood and eliminating other causes of a high uric acid, such as food, exercise, nephritis, etc. With these ruled out the uric acid must be derived from some focus of infection from which a constant stream of nucleoprotein and purin material is being poured into the blood stream.

The amount of uric acid in the blood depends on the area and degree of absorption from the above mentioned sources. We have seen the high uric acid of several patients drop to normal after the removal of areas of absorption, as in infected tonsils, gangrenous toe, alveolar abscesses, necrotic epitheliomas, etc., absorption from the areas of degenerating material undoubtedly being the cause of the high uric acid content in each case.

With these simple, well known facts in mind, we included the observation of the uric acid in the blood in our roentgen-ray study, believing that a temporary and possibly a permanent change could be produced in an individual exposed to the rays. All cancer cases do not necessarily have a high uric acid content in the blood, especially where the tumor is uninfected. If, however, there has been infection of the mass with central necrosis, the uric acid is increased directly in proportion to the amount of absorption of nucleoprotein material.

Of the thirty-six patients studied, only two had a normal uric acid in the blood before roentgen-ray exposure. In twenty cases the uric acid was increased, one-half hour after roentgen-ray exposure, and in sixteen cases it was lower after than before such exposure. Fourteen of these sixteen cases had an excessively high uric before roentgen-ray treatment. On the day following treatment, twenty patients still had a high uric acid, in fifteen the uric acid was lower than before roentgen-ray exposure and in the remaining case the uric acid was unchanged. Of the fourteen cases in which the uric acid was lower on the day following roentgen-ray exposure, four patients were becoming worse, two were improving, four were operated on with no recurrence, one patient, a control case, was not subjected to roentgen-ray treatment. Of the twenty-two patients having an increased uric acid content the day after roentgen-ray exposure, one was becoming worse, four were improving, two were operated on with no recurrence, three were clinically well, one patient left and has not returned, one patient is a normal roentgen-rayed control. The



three noncancerous control persons were not exposed to the rays quite as long as were the patients. They had a lower uric acid content on the day following roentgen-ray exposure. Four of the patients studied have since died from their cancers, three having a very high uric acid content on the day following roentgen-ray exposure and the other remaining unaltered.

There is no relation between the progress of the patient and the uric acid in the blood. Roentgen rays can be said to increase the uric acid content of the blood only by destruction of tissue or by causing a leukocytosis with subsequent destruction of leukocytes producing a uric acid increase for a short period of time. The effect of the roentgen ray varies in different individuals, some getting a more severe reaction than others, so that the amount of increase of uric acid in the blood depends on the dosage of roentgen rays, the condition of the tumor and the condition of the patient. Here, neither an increase nor a decrease in uric acid is permanent. It may last a few hours or a few days.

Rosenberg, in 1906, observed the uric acid excretion in leukemias and some other diseases. He reported on increased excretion in the leukemias only. No blood studies were made at the time, but there must have been with the increase in urinary excretion a corresponding increase in the uric acid content of the blood.

#### CHLORIDS

The normal range of chlorids in the blood as sodium chlorid varies from 400 mg to 650 mg. Five of our patients had a chloridemia of more than 650 mg before treatment. They had either mouth or laryngeal or esophageal cancers and drank very little water. These same individuals had high corpuscle percentages and none of them were in any marked degree nephritic.

Thirty-five patients had normal blood chlorids before roentgen-ray exposure. One half-hour after roentgen-ray treatment the chlorids were slightly increased in quantity in sixteen cases, decreased in twenty cases and unchanged in four cases. Of these cases, five only were out of normal limits. Twenty-four hours after exposure, fifteen patients still had a higher chlorid content than they had before being rayed, and in twenty patients it was lower.

The total range of chlorid concentration was within normal limits in all but six cases, in five of these it was abnormally high during the whole period of observation, due to the low fluid intake, and in one

case the chlorid content had increased from normal to a hyper-chloridemia on the day following treatment

The sodium chlorid content of the blood of cancer patients is normal, and is unaffected by roentgen rays

TABLE 4—CHLORID CONTENT OF THE BLOOD  
Mg per 100 c c

Number	Before Roentgen-Ray Exposure Per Cent	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent
1	450 0	475 0	337 5
2	437 5	413 0	450 0
3	525 0	400 0	437 5
4	563 0	400 0	475 0
5	437 5	437 5	425 0
6	412 0	437 5	437 5
7	437 5	437 5	437 5
8	425 0	475 0	487 0
9	425 0	450 0	425 0
10	275 0	437 5	500 0
11	400 0	437 5	423 5
12	463 5	375 0	500 0
13	475 0	463 5	463 5
14	475 0	435 0	437 5
15	463 5	437 5	450 0
16	475 0	435 0	700 0
17	720 0	800 0	600 0
18	712 5	850 0	993 5
19	337 5	428 0	462 5
20	337 8	312 5	487 5
21	462 5	500 0	425 0
22	500 0	600 0	463 0
23	425 0	475 0	512 5
24	525 0	412 0	475 0
25	437 5	437 5	425 0
26	250 0	475 0	550 0
27	375 0	275 0	425 0
28	432 5	412 5	462 5
29	475 0	437 5	462 5
30	450 0	462 5	239 5
31	460 0	425 0	460 0
32	650 0	600 0	620 0
33	700 0	667 0	687 5
34	362 5	562 5	437 5
35	462 5	635 0	463 5
36	563 0	475 0	475 0
37	525 0	400 0	
38	703 0	705 0	
39	875 0	925 0	
40	450 0	435 0	
41	375 0	387 5	

#### CHOLESTEROL

Cholesterol was discovered in gallstones by Conradi, in 1775, and named, in 1815, by Chevreul and since that time very little progress has been made until during the last fifteen years, when with newer

and more accurate methods, comparative studies have been possible. Physiologists practically all agree now that cholesterol is ingested with the food, liberated in the intestinal tract, is then esterized and

TABLE 5—CHOLESTEROL CONTENT OF BLOOD  
Mg per 100 c c

Number	Before Roentgen Ray Exposure Per Cent	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent
1	121 0	115 0	287 0
2	125 0	156 2	130 0
3	233 0	198 0	265 0
4	267 0	198 0	250 0
5	163 0	187 0	375 0
6	175 0	187 5	69 3
7	175 0	178 0	175 0
8	94 0	175 0	109 0
9	120 0	125 0	150 0
10	160 0	234 0	175 0
11	208 0	269 0	250 0
12	187 5	312 5	312 5
13	137 0	189 0	269 0
14	185 0	144 0	125 0
15	178 0	320 0	312 0
16	138 0	125 0	187 0
17	208 3	208 3	208 3
18	179 0	108 7	*
19	107 75	237 3	250 0
20	133 8	84 0	104 0
21	156 2	187 5	178 5
22	208 0	234 0	208 0
23	187 5	226 0	210 6
24	288 0	170 4	208 3
25	175 0	104 0	93 0
26	187 0	133 0	133 0
27	156 0	187 0	133 0
28	98 0	156 2	156 2
29	67 0	156 2	162 5
30	134 0	156 2	187 5
31	180 0	250 0	270 0
32	208 3	250 0	163 0
33	191 3	150 0	144 2
34	173 6	173 6	185 6
35	102 9	183 8	208 3
36	200 0	234 0	234 0
37	187 0	395 0	*
38	175 0	175 0	*
39	208 3	208 3	*
40	150 0	187 5	*
41	208 3	187 5	*

\* No estimation made

absorbed by the lymphatics to be delivered to the blood stream and so distributed to the body cells. This exogenous source of cholesterol is the largest and most important one. Later, as these cells die and become autolyzed, their content of cholesterol is again delivered to

the blood stream, removed by the liver, excreted through the bile and in large part reabsorbed, thus forming the endogenous source of cholesterol, if it may be so called <sup>4</sup> There is no proof that cholesterol may be synthesized in the body In the egg it has been shown that there is no gain in cholesterol during the incubation of the chick <sup>5</sup> The body depots for blood cholesterol are the skin, eye tissues, biliary vesicles and the atheromatous areas of arteries

Ignatowski, of the Russian school at St Petersburg, first observed tissue lesions resulting from abnormal foods He suspected animal proteins to be the cause of the injury Stuckey<sup>6</sup> showed that egg white and meat juice, fat and lecithin had no effect, but that cholesterol gave uniform results It caused an increased endothelial activity, the arteries of the lung tissue showing the greatest arterial changes, then those of the kidney, heart and spleen The suprarenal cortex, liver cells and intima of arteries act as intermediate organs for the final disposal of cholesterol esters

In man as in animals the excretion of cholesterol in the feces can be accounted for by that taken in with the food when the body weight remains constant If, however, a rapid loss in weight takes place, the output of cholesterol exceeds the intake <sup>7</sup> This total and free cholesterol is very constant per kilogram of body weight On forced cholesterol feeding or in a marked cholesterinemia considerable cholesterol has been found in the suprarenals as well as in the liver This fact gives rise to the question as to how much the suprarenals have to do with the cholesterol metabolism The liver and not the adrenals is the chief organ for the control of cholesterol metabolism according to one author <sup>8</sup> Luden believes that faulty metabolism causing high cholesterol in the blood, is closely associated with cell proliferation She says that the integrity of the liver function plays an important and probably prominent part in the etiology of malignant disease She has shown that a patient with a malignant proliferation in the liver gives the highest cholesterol values in the blood <sup>9</sup>

In this study it was our intention to compare the cholesterol content of the blood of cancerous people with normals, and to ascertain whether roentgen-ray exposure alters this content in any way

Forty-one cases were studied Before roentgen-ray treatment, twenty-three patients had a hypercholesterinemia, thirteen were normal One-half hour after roentgen-ray treatment, twenty-five had

4 Taylor Digestion and Metabolism, 1912

5 Doree and Gardner Proc Roy Soc, Lond **81** 1909

6 Klotz, O Med Res, **33** 157 (Nov) 1915

7 Ellis, G W, and Gardner Proc Roy Soc, Lond **86** 13, 1913

8 Rothchild, M A Proc N Y Path Soc **14** 229, 1914

9 Stewart, M J J Path & Bact **19** 305, 1914

reached a higher cholesterol figure than before, in three the cholesterol was unchanged, and in thirteen the cholesterol blood content was lower. Twenty-four hours after roentgen-ray treatment the cholesterol content in twenty cases had reached a higher figure, in six cases a third estimation was not made, in three cases the cholesterol content was unchanged, and in twelve cases it was lower than normal. One-half hour after treatment the cholesterol content was higher in eleven cases, unchanged in six and lower in nineteen cases. In six cases no estimation was made. We are unable to draw any definite conclusions from these results in regard to the size or type of tumor, its location or the duration of the exposure to the rays. On the other hand, one-half hour after roentgen-ray treatment, we find that in 61 per cent of our series of forty-one cases the cholesterol figures were higher than they were before treatment. In 31 per cent of the cases the cholesterol content was lower than before treatment. The findings twenty-four hours afterward are not any more conclusive but they are of interest in that they indicate the ability of the organism to handle an excess of cholesterol. Whether this is an index of one of the functions of the liver or simply of a lowered ability of the tissues to combine with the cholesterol, we cannot say. We can say, however, that exposure to roentgen ray in the majority of cases causes an increase in cholesterol content in the blood, although this increase is not proportional to the time of exposure or the type of tumor. It probably is due to the autolysis of the cells by the rays, resulting in the liberation of this substance.

#### FATTY ACIDS

If we take 500 mg as the high normal of fatty acids, we find that in thirty-six cases, or 90 per cent, the fatty acid content of the blood is higher than normal before roentgen-ray treatment. One-half hour after exposure, an increase in the fatty acids was found in thirty-four cases, or 83 per cent, a decrease from the first estimation in thirty-five cases, or 61 per cent, an increase over the first estimation in twelve cases, or 31 per cent, and in three cases, or 8 per cent, the amount of fatty acids was practically unchanged. Twenty-four hours after exposure there was an increase in the fatty acids in the blood in twenty-eight cases, or 80 per cent, a decrease from the first estimation in twenty-six cases, or 72 per cent, and an increase from the first estimation in six cases, or 16 per cent.

It is evident that this series of cancer cases has a very high percentage of increased fatty acids in the blood, and that this percentage is reduced by roentgen-ray exposure. In most of these cases, the

decrease was noted one-half hour after the exposure, although the percentage of cases showing decreased fatty acids was still larger at the end of twenty-four hours. We can say, therefore, that roentgen-ray exposure oxidizes the fatty acids and that the results of this

TABLE 6—FATTY ACIDS IN THE BLOOD  
Mg per 100 c c

Number	Before Roentgen Ray Exposure Per Cent	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent.
1	788 0	702 0	405 0
2	774 0	677 8	704 0
3	943 0	1340 0	687 0
4	785 0	978 0	659 0
5	746 0	813 0	375 0
6	480 0	479 1	643 9
7	658 2	562 0	565 0
8	798 8	538 2	557 0
9	620 0	481 0	505 0
10	515 0	430 0	400 0
11	1354 0	1397 0	831 0
12	1553 5	739 5	687 5
13	1681 0	2033 0	631 9
14	1114 0	1376 0	927 0
15	998 0	930 0	789 0
16	2084 0	1087 0	527 0
17	947 7	849 7	757 7
18	1000 0	917 0	1149 0
19	1086 0	909 0	909 0
20	1438 0	1117 0	966 0
21	1271 8	1351 5	1271 5
22	968 0	675 0	792 0
23	1351 5	683 0	789 4
24	823 0	940 6	591 7
25	459 0	784 8	713 4
26	436 0	481 0	533 0
27	533 0	479 0	527 0
28	795 0	612 8	647 8
29	706 0	612 8	912 5
30	735 0	584 8	479 5
31	772 0	720 0	668 0
32	940 7	879 0	1020 0
33	774 7	788 0	780 0
34	1116 4	527 4	743 4
35	846 1	566 2	591 7
36	436 0	345 0	442 0
37	722 0	909 0	*
38	*	*	*
39	687 7	604 7	*
40	683 0	1293 5	*
41	606 7	923 5	*

\* No estimation

last at least twenty-four hours. Further than this we do not care to express ourselves at present. At a future date we hope to have a more complete series of fat studies and to be able to draw a more definite conclusion.

## TOTAL FATS

The digested fat of the diet is split into glycerol and fatty acids, which recombine in the cells of the intestinal mucosa into the original fat. The greater part of the fat is then collected in the lacteals and

TABLE 7—TOTAL FATS IN THE BLOOD  
Mg per 100 c.c. of blood

Number	Before Roentgen Ray Exposure Per Cent	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent
1	909 0	817 0	692 0
2	909 0	834 0	834 0
3	1176 0	1538 0	952 0
4	1052 0	1176 0	909 0
5	909 0	1000 0	754 0
6	655 0	666 6	713 2
7	833 3	740 0	740 0
8	892 8	713 2	666 0
9	714 0	606 0	655 0
10	657 0	664 0	606 0
11	1562 0	1666 0	1081 0
12	1741 0	1052 0	1000 0
13	1818 0	2222 0	900 9
14	1299 0	1520 0	1052 0
15	1176 0	1250 0	1111 0
16	2222 0	1212 0	714 0
17	1156 0	1058 0	966 0
18	1000 0	919 0	1149 0
19	1086 0	909 0	909 0
20	1438 0	1117 0	966 0
21	1428 0	1539 0	1450 0
22	1176 0	909 0	1000 0
23	1538 0	909 0	1000 0
24	1111 0	1111 0	800 0
25	634 0	888 8	806 4
26	623 0	614 0	666 0
27	689 0	666 0	660 0
28	893 0	769 0	834 0
29	773 0	769 0	975 0
30	869 0	741 0	667 0
31	952 0	970 0	938 0
32	1149 0	1129 0	1183 0
33	960 0	938 0	925 0
34	1290 0	701 0	909 0
35	950 0	740 0	800 0
36	636 0	579 0	676 0
37	395 0	1000 0	*
38	*	*	*
39	896 0	813 0	*
40	833 0	1481 0	*
41	815 0	1111 0	*

\*No estimation

appears in the thoracic duct as an emulsion which is eventually emptied into the blood. The portion of fat not absorbed by the lacteals enters the portal circulation directly as a fine suspension. This fat

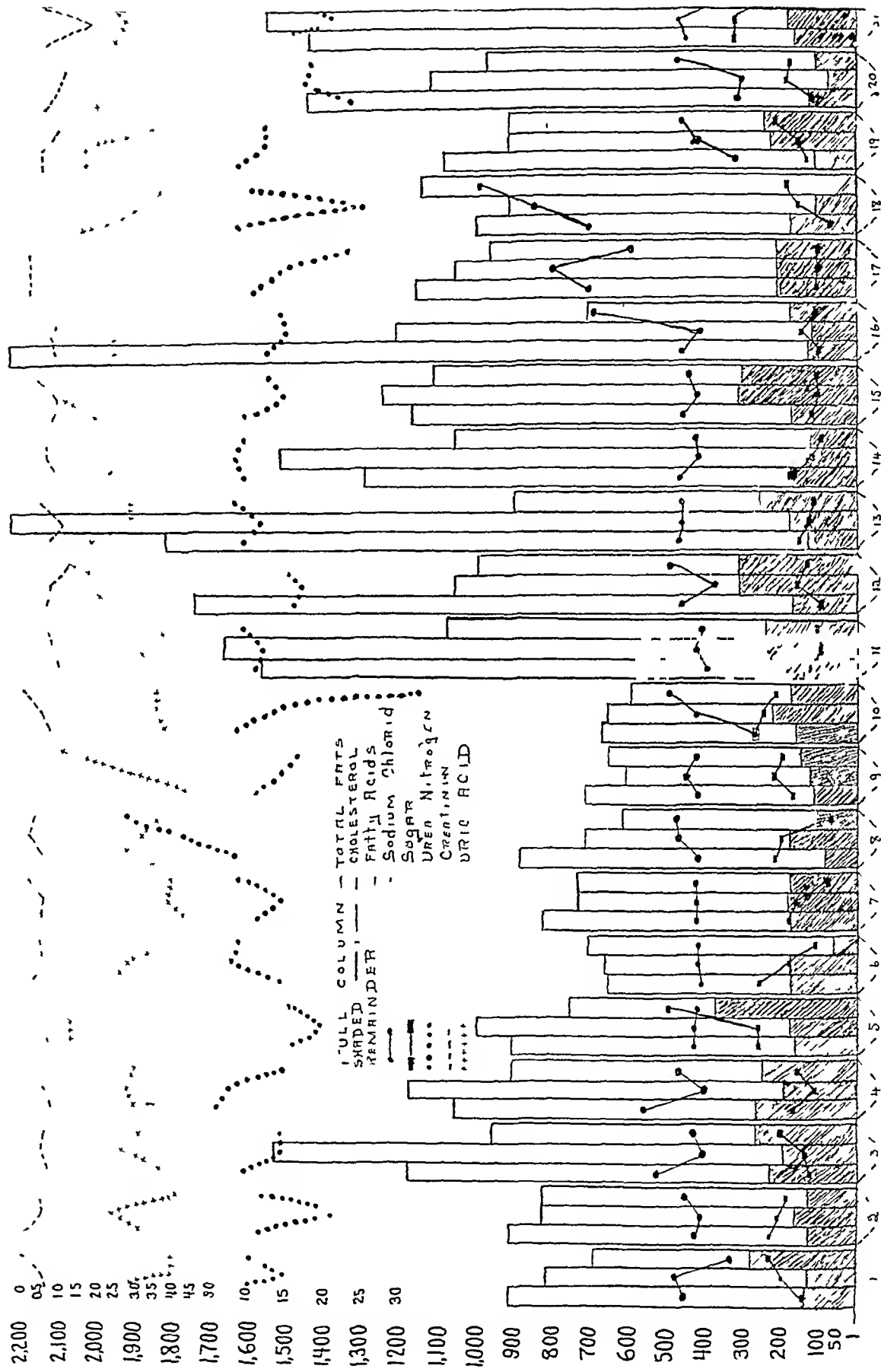
is then slowly removed from the blood stream to be stored up in the organism as depot fat, in its original form, for one type of fat cannot be converted into another type. Later on, the cells of the body, especially the erythrocytes, take up this fat from the plasma and transform it into lecithin<sup>10</sup> which is an intermediate product in fat metabolism. Fat is also formed from sugar. This is the specific body fat and is stored in the connective tissues and liver until it is utilized. Then, there is a small percentage of a fat protein combination to be considered. In malignancy, with its attending cachexia, so common in the majority of cases, digestion and absorption of fats are normal, but there is very little, if any, fat storage. It is difficult to arrive at a general average of the normal limits for the total fats in the blood. So much depends on the time of collection of blood in relation to meals, the amount and type of food, and the rapidity of digestion. However, as the bloods in this series were collected between nine and ten in the morning, one-half hour after the roentgen-ray exposure, and finally twenty-four hours afterward, we shall consider 700 mg. as being the normal amount of total fats.

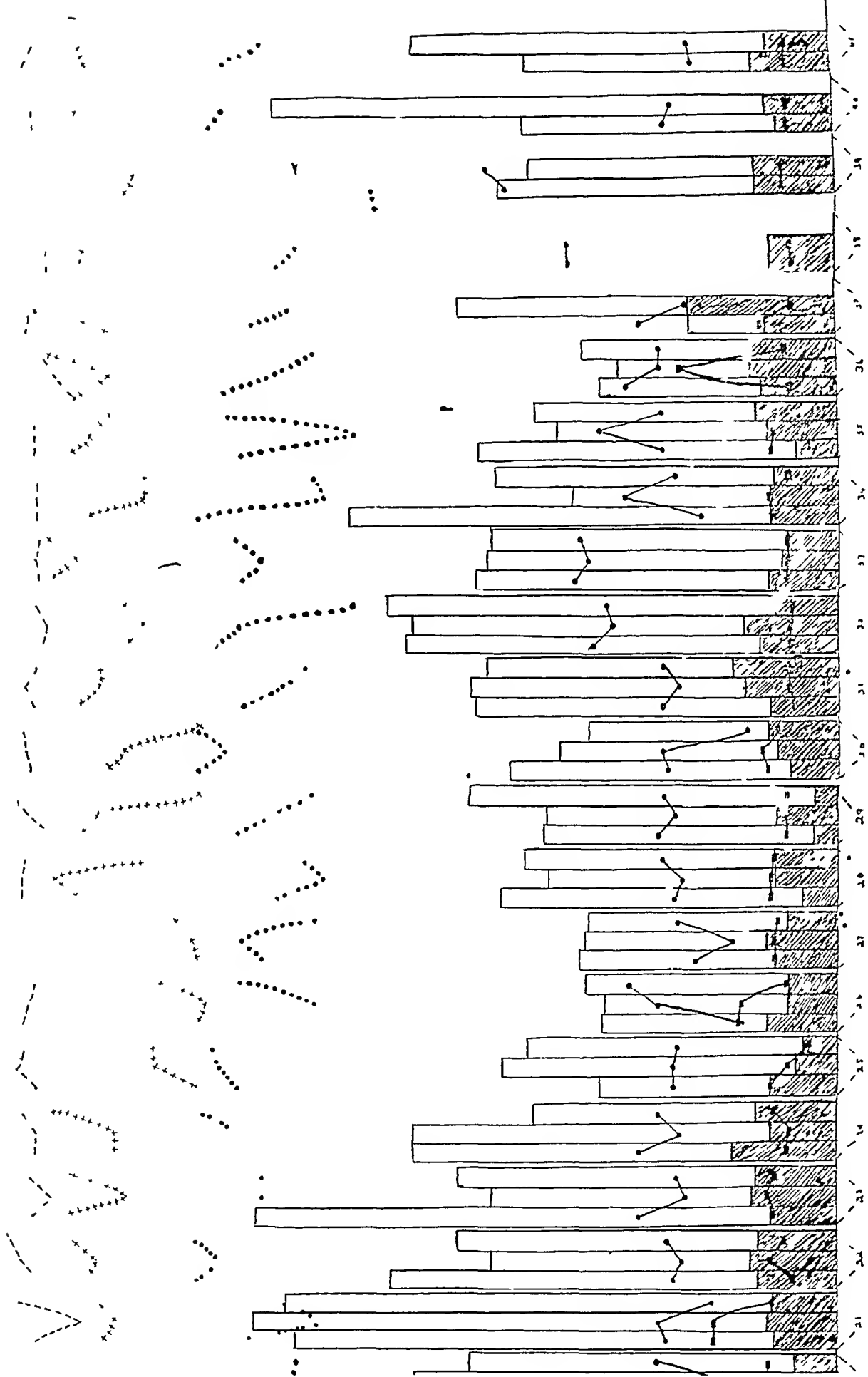
Of forty-one cases studied, thirty-four, or 83 per cent, showed a varying excess of total fat in the blood before exposure to the roentgen rays. One-half hour after exposure to the roentgen rays, the first findings were increased in thirteen cases, and decreased in twenty-eight cases. Twenty-four hours after treatment with the roentgen ray, the first findings were increased in six cases and decreased in thirty cases. Thus, the total fat content was diminished in 83 per cent of this series of cases after exposure to the roentgen ray and in some cases the decrease was preceded by a slight rise of the total fat quantity.

To what is this due? (a) To an inability of the cells to remove this suspension of fat from the blood? In this respect one notices in all cachectic states an almost constant milky appearance of the serum, or a lipemia. (b) Or is this low or absent fat storage due to the fact that these cells cannot convert the blood suspension into a state suitable for storage?

Again, we can conclude, as in the case of the fatty acids, that there is a definite increase in the blood fat which is markedly reduced for at least twenty-four hours after exposure to the roentgen rays, but we withhold any further conclusions till we have finished our more conclusive study.







Over a period of long observation we have taken the normal limits of blood sugar to be from 90 to 150 mg. Twenty of our subjects had a blood sugar content of more than 150 mg. which we ascribe to high carbohydrate diet and too little exercise, for the

TABLE 8—SUGAR CONTENT OF THE BLOOD  
Mg per 100 c c

Number	Before Roentgen Ray Exposure Per Cent	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent
1	143 0	190 0	235 0
2	222 0	210 0	181 0
3	133 0	142 0	200 0
4	160 0	114 0	153 0
5	266 0	266 0	500 0
6	256 4	178 0	111 0
7	185 0	166 0	80 0
8	222 0	200 0	68 0
9	174 0	222 0	200 0
10	261 0	250 0	217 0
11	133 0	100 0	118 0
12	100 0	160 0	143 0
13	154 0	143 0	133 0
14	182 0	121 0	100 0
15	143 0	121 0	133 0
16	108 0	154 0	127 0
17	117 0	117 0	117 0
18	80 0	154 0	190 0
19	142 0	153 0	220 0
20	123 0	190 4	178 0
21	333 0	333 0	166 0
22	123 0	188 0	143 0
23	164 0	181 0	166 0
24	133 0	123 0	166 0
25	174 0	143 0	87 0
26	266 0	250 0	142 0
27	166 0	166 0	153 0
28	182 0	182 0	175 0
29	143 0	143 0	143 0
30	190 0	200 0	153 0
31	117 0	133 0	137 0
32	130 0	130 0	125 0
33	140 0	140 0	142 0
34	160 0	166 0	133 0
35	188 0	181 8	152 0
36	135 0	427 0	137 0
37	200 0	111 0	
38	115 0	121 0	
39	143 0	143 0	
40	133 0	133 0	
41	130 0	130 0	

bed patient always shows deficient oxidative powers. We had one diabetic (Case 5) with a glycosuria in the series. Of the patients studied, several had slight renal lesions, but the majority were normal as to blood chemistry.

Before roentgen-ray treatment, seven patients had hyperglycemia, twenty-one had normal sugar. One-half hour after roentgen-ray treatment, fourteen patients had increased blood sugar, sixteen had decreased sugar, and in ten cases the blood sugar was unchanged. Twenty-four hours after roentgen-ray treatment, fifteen patients had

TABLE 9—DIASTATIC FUNCTION OF BLOOD

Number	Before Roentgen Ray Exposure Per Cent	One Half Hour After Roentgen Ray Exposure Per Cent	Twenty Four Hours After Roentgen Ray Exposure Per Cent
1	11	42	34
2	28	30	22
3	11	12	10
4	8	8	28
5	19	60	60
6	29	14	11
7	30	44	13
8	28	17	17
9	65	12	10
10	28	17	36
11	38	50	21
12	20	34	18
13	13	21	23
14	13	11	37
15	10	6	25
16	46	49	54
19	51	48	17
20	28	62	14
21	47	13	33
22	32	7	28
23	47	44	47
24	26	30	14
25	44	44	18
26	47	22	15
27	47	33	69
28	20	30	38
29	21	3	9
30	34	32	58
34	48	50	40
35	31	43	36
36	38	96	12
37	10	17	
40	28	28	
41	40	40	

increased blood sugar, eighteen had a decreased blood sugar, and in two cases the blood sugar content was unchanged. In the cases in which the blood sugar content was lowest following roentgen-ray treatment, the patients had received the largest doses, so we can say that the roentgen ray increases the oxidation of blood sugar. This is true of any individual whether he has had malignant disease or not. The

degree of oxidation brought on by the roentgen ray is undoubtedly dependent on the degree of hyperglycemia and the duration of the exposure. The effect is not permanent, and a low blood sugar is not further oxidized, but, on the other hand, is increased.

#### DIASTATIC ACTIVITY OF BLOOD

In one half of the cases the diastatic activity of the blood had increased one-half hour after exposure and in the other cases there was a decrease of diastatic activity. The next day the diastatic activity of one half of the cases studied had increased and in the remainder it had decreased. As the diastatic activity of subjects treated under similar conditions did not show a consistent behavior, we can say that the roentgen rays have no special or permanent effect on the diastatic activity of the blood.

#### CORPUSCLE AND PLASMA PERCENTAGE

The normal plasma and corpuscle volumes vary between 45 and 55 per cent. Ten c.c. of oxalated blood were centrifuged for five minutes and the percentage of corpuscles and plasma were read directly from the graduations on the tube. The centrifuging was done in each instance at the same rate of speed and for the same period of time. We found that longer centrifuging does not appreciably decrease the corpuscle percentage, and a tube of the oxalated blood standing upright in the icebox gives the same reading of corpuscle percentage.

Before roentgen-ray exposure, ten patients had a low corpuscle percentage, five had a high percentage, and in twenty-one it was normal. Of these twenty-one subjects the corpuscle percentage was decreased in four one-half hour after they were exposed to the roentgen ray and also on the following day, three subjects had an increased corpuscle percentage one-half hour afterward, and five subjects showed an increase the day after treatment. In sixteen subjects the corpuscle percentage remained normal one-half hour after exposure, and in eleven subjects the percentage was still normal the day after exposure. Patients with a low corpuscle percentage were usually anemic. Twenty-four hours after roentgen-ray treatment, eight subjects had a higher corpuscle percentage, fifteen had a decreased percentage and in eleven it remained normal.

Nothing of particular interest was observed in this study, except that the corpuscles quickly settle to their actual volume, and long centrifuging does not pack them any tighter. There is nothing characteristic of the cancer patient in the corpuscle percentage, which

usually varies with the anemia. Some of the patients were unable to drink much water, consequently the corpuscle percentage was high, although there was a marked degree of anemia.

TABLE 10—PLASMA AND CORPUSCLE PERCENTAGE  
Volume percentage

Number	Before Roentgen-Ray Exposure		One Half Hour After Roentgen Ray Exposure		Twenty Four Hours After Roentgen Ray Exposure	
	Plasma	Corpuscles	Plasma	Corpuscles	Plasma	Corpuscles
	%	%	%	%	%	%
1	52	48	50	50	47	53
2	54	46	54	46	54	46
3	50	50	50	50	53	47
4	50	50	50	50	50	50
5	55	45	55	45	66	34
6	53	47	55	45	55	45
7	62	38	69	31	59	41
8	50	50	55	45	50	50
9			35	65	32	68
10	52	48	53	47	45	55
11	50	50	50	50	50	50
12	48	52	48	52		
13	50	50	50	50	50	50
14	50	50				
15	50	50	50	50		
16	48	62	50	50	50	50
17	50	50	50	50	50	50
18	54	46	50	50	50	50
19	72	28	56	44	58	42
20	48	52	48	52	50	50
21	48	52	45	55	45	55
22	48	52	48	52	32	68
23	60	40	50	50	52	48
24	46	54	46	64	50	50
25	62	38	60	40	75	25
26	34	66	27	73	30	70
27	44	56	50	50	41	39
28	40	60	40	60	44	56
29	50	50	50	50	43	57
30	50	50	50	50	50	50
31	28	72	26	74	40	60
32	50	50	40	60	45	55
33	67	43	50	50	50	50
34	57	43	60	40	60	40
35	56	44	58	42	61	39
36	67	33	50	50	50	50
37	57	43	60	40		
38	28	72	30	70		
39	65	35	69	31		
40	50	50	50	50		

#### SYNOPSIS OF CASE REPORTS

All roentgen-ray treatments were applied directly to the lesion, except in Cases 6 and 25, in which the spleen was treated, and Case 27, in which the abdomen was treated. The control subjects, Cases 12, 16 and 27, were not treated. One patient, Case 23, was given radium

treatment Cases 22, 24 and 27 were nurses in a fairly good state of health They received small doses of the roentgen ray

CASE 1 (5462)—Male, age 50, well Epithelioma of glans penis, removed at operation, Aug 7, 1917 Lymph nodes in both femoral and inguinal regions enlarged Uncle had carcinoma of lip Received seven roentgen-ray treatments during ensuing year Discharged clinically well Six treatments had been given before the blood study was made Filter, 14, ma/v, 5/90, time, 7', distance, 25.5 cm

CASE 2 (5519)—Female, age 60 Progressing adenocarcinoma of left hand for two years, and of right hand for thirteen years, probability of metastatic nodes in lower lobes of both lungs Definite tumor mass in right lower abdomen Received three roentgen-ray treatments on hands Lesions healed, but general condition is growing worse One treatment was given previous to present study No filter, ma/v, 10/90, time, 2' 40", distance, 20.4 cm

CASE 3 (5533)—Female, age 57, died Primary carcinoma of left breast Nodes in supraclavicular and infraclavicular fossae enlarged and movable Metastatic nodes in left axilla Maternal aunt had cancer of eye Received twelve roentgen-ray treatments The first treatment was given at the time the blood study was made Filter, 14, ma/v, 7/90, time, 10', distance, 20.4 cm

CASE 4 (5526)—Male, age 65, improved Epithelioma of left temple Had paralytic stroke two years ago Received fifteen roentgen-ray treatments four of which preceded the one given at the time of the blood study Filter, 14, ma/v, 5/90, time, 10', distance, 20.4 cm

CASE 5 (5467)—Male, age 61, died Endothelioma of right parotid region and diabetes Metastases in submental nodes Received twelve roentgen-ray treatments, the twelfth being the one given at the time of the blood study Filter, 14, ma/v, 7/90, time, 7', distance, 20.4 cm Died in diabetic coma Necropsy Chronic interstitial and parenchymatous nephritis, bronchopneumonia, carcinoma, probably epithelioma, of parotid

CASES 6 AND 38 (5357)—Male, age 70 years, died Epithelioma of left side of head, following injury Left ear sloughed off Received thirty-two roentgen-ray treatments before the one given with the blood study Filter, 14, ma/v, 3/90, time, 5', distance, 25 cm Necropsy Abscess of lung and metastatic growths, nutmeg liver, mild chronic nephritis, lymph node tumor metastasis (This is also Case 38)

CASE 7 (5524)—Female, age 30, improved, exophthalmic goiter One roentgen-ray treatment given before special study Filter, 14, ma/v, 5/90, time, 7', distance, 20.4 cm

CASE 8 (5536)—Male, age 31, unimproved Abdominal tumor Received one roentgen-ray treatment Filter, 14, ma/v, 5/90, time, 10', distance, 20.4 cm

CASE 9 (5253)—Male, age 24, improved Sarcoma of left foot following injury Received twenty-six roentgen-ray treatments, one preceding that of the blood study Filter, 14, ma/v, 7/90, time, 7', distance, 20.4 cm

CASE 10 (5513)—Female, age 65, died Carcinoma of left breast, removed at operation Metastasis advanced Four roentgen-ray treatments after operation Filter, 14, ma/v, 7/90, time, 7', distance, 20.4 cm Necropsy Metastases in nodes of mediastinum and hylum of lung Bronchopneumonia in lungs, cloudy swelling of kidneys and fatty infiltration of liver Tumor is carcinoma

CASE 11 (5636)—Male, age 58 Tumor of lung, operated and abscess drained Died three months later Received seventeen roentgen-ray treatments, eleven before this study Filter, 14, ma/v, 7/90, time, 7', distance, 20.4 cm

CASE 12 (5027)—Female, age 54, recovered Carcinoma of left breast, following abscess in breast Removed at operation Received twenty-four post-operative roentgen-ray treatments before this study This was a control case

and the blood was withdrawn at stated intervals without roentgen-ray exposure at the time Filter, 13, ma/v, 14/90, time, 5', 10", distance, 20 cm

CASE 13 (5404)—Female, age 50 years, improved Carcinoma of right breast, removed at operation Received two roentgen-ray and three radium treatments, postoperative Roentgen ray, filter, 14, ma/v, 7/90, time, 5', distance, 25.5 cm

CASE 14 (5528)—Female, age 52 Recurrence Carcinoma of left breast, removed at operation Ten roentgen-ray treatments and one radium treatment The radium treatment preceded the first roentgen-ray treatment which was the one of our study Filter, 14, ma/v, 7/90, time, 8', 10", distance, 20.4 cm

CASE 15 (5470)—Male, aged 71 Stationary carcinoma of bladder, post-operative, and carcinoma of prostate Received twenty-two roentgen-ray treatments, twelve before the blood study Filter, 14, ma/v, 7/90, time, 7', distance, 20.4 cm

CASE 16 (5190)—Male, aged 59, clinically well Lymphosarcoma of right tonsil One radium treatment, twenty-eight roentgen-ray treatments Control case Blood withdrawn at intervals without roentgen-ray treatment

CASE 17 (5500)—Female, age 62, unimproved Epithelioma of left shoulder, following injury Received four roentgen-ray treatments, the one of this study being the first No filter, ma/v, 10/90, time, 2' 13", distance, 20.4 cm

CASE 18 (5494)—Male, age 55 Progressing epithelioma of lower lip Nodes of submaxillary and submental regions enlarged Fifteen roentgen-ray treatments given, the first one being at the time of the blood study Filter, 0, ma/v, 10/90, time, 2' 13", distance, 20.4 cm

CASE 19 (5504)—Male, aged 57, no improvement Epithelioma of left ear Mother died from cancer of forehead at 60 Received eight roentgen-ray treatments, two before the blood study, and one radium treatment Filter 0 to 14, ma/v, 10/90-7/90, time, 2' 19", distance, 20.4 cm (This is also Case 40)

CASE 20 (5511)—Female, aged 66, well Epithelioma of nose Eight roentgen-ray treatments were given, the first one with the blood study Filter, 0, ma/v, 10/90, time, 2' 39", distance, 20.4 cm

CASE 21 (5518)—Male, aged 31, well Adenocarcinoma of cecum, removed at operation Received seven roentgen-ray treatments, two before the one with the blood study Filter, 14-24, ma/v, 7/90, time, 7'-10', distance 20.4 cm

CASE 23 (5507)—Female, aged 44, improving Carcinoma of cervix uteri Postoperative One radium treatment only

CASE 25 (5158)—Female, aged 60, died Recurrence of carcinoma of right breast, two years after operation Thirty-three roentgen-ray treatments over spleen, twenty-three before present study Filter, 14, ma/v, 3/90, time, 5', distance, 25 cm Necropsy Metastasis in kidneys, liver, lymph nodes and lung Suprarenals sclerotic, yellow atrophy of heart

CASE 26 (5522)—Male, aged 35, cured Angioma of lower lip Removed under local anesthesia One roentgen-ray treatment on abdomen Filter, 14, ma/v, 7/90, time, 7', distance, 20.4 cm

CASE 28 (5520)—Male, aged 52, cured Epithelioma of left temple, excised Received two roentgen-ray treatments, the first being at the time of this study Dose No filter, ma/v, 10/90, time, 2' 40", distance, 20.4 cm

CASE 29 (5488)—Male, aged 46 Epithelioma lower lip, no recurrence Excised Two roentgen-ray treatments, the first given at the time of this study Filter, 14, ma/v, 7/90, time, 7', distance, 25.5 cm

CASE 30 (5475)—Male, aged 51, unimproved Sarcoma of neck Fourteen roentgen-ray treatments given, one before this study Filter, 14, ma/v, 7/90, time, 5', distance, 20.4 cm



CASE 31 (5302) —Male, aged 50, died at home Fibrosarcoma of left parotid region Fifty-one roentgen-ray treatments, sixteen of them before present study and one radium treatment Filter, 14, ma/v, 7/90, time, 5', distance, 20.4 cm

CASE 32 (5223) —Female, aged 58, unimproved Carcinoma of right breast, two years' duration Removed at operation Fifty-three postoperative roentgen-ray treatments, sixteen before present study Filter, 14, ma/v, 7/90, time, 7', distance, 20.4 cm

CASE 33 (5412) —Male, aged 58, died Epithelioma Left face and ear, twenty years' duration Left ear sloughed with wide ulceration Eighteen roentgen-ray treatments given, fifteen before present study No filter, ma/v, 10/90, time, 2' 13", distance, 25.5 cm

CASE 34 (5427) —Male, aged 82, unimproved Epithelioma of left nasal cavity with erosion of left nasal bone Ten radium and two roentgen-ray treatments given, one before present study Filter, 14, ma/v, 7/90, time, 5', distance, 20.4 cm

CASE 35 (5501) —Male, aged 65, unimproved Epithelioma of right eye Fifty-two years' duration Received three roentgen-ray treatments, the third at the time of this study Filter, 14, ma/v, 7/90, time, 10'

CASE 36 (5505) —Male, aged 37, died Melanosarcoma left groin with metastasis Received one roentgen-ray treatment Filter, 14, ma/v, 7/90, time, 7', distance, 20.4 cm

CASE 37 (5535) —Male, aged 27, clinically well Granuloma syphilid with possibly Hodgkin's disease Received two roentgen-ray treatments here and fifty at another institution, all before the treatment of the present study

CASE 39 (5485) —Female, aged 39, unimproved Carcinoma of cervix and vagina, postoperative Received two radium treatments before the roentgen-ray exposure of this study Filter, 14, ma/v, 7/90, time, 35', distance, 20.4 cm.

CASE 41 (5276) —Male, aged 41, unimproved Epithelioma lower lip. Received eighteen roentgen-ray treatments, three before present study Filter, 4, ma/v, 7/90, time, 10'

#### CONCLUSIONS

Our object in this paper has been to note the effect of roentgen rays on cancer patients, as manifested by changes in their blood chemistry, and to continue investigation of the individual blood factors where it seemed to be indicated

1 Urea, urea nitrogen and creatinin show nothing characteristic of the cancer patient

2 The moderate uric acidemia which exists for a short period of time after exposure to roentgen rays is the result of nuclear degeneration but is not especially characteristic of malignancy

3 The sodium chlorid content of cancer patients is altered neither by the presence of the tumor nor the exposure to roentgen rays

4 The cholesterol, fatty acids and total fats are generally increased in cases of malignancy Cholesterol is increased in the blood, but this is not in proportion to the duration of exposure to the roentgen ray or varied as to the type of tumor The increase of cholesterol in the blood is probably due to cellular autolysis with liberation of cholesterol, induced by the action of the roentgen rays Fatty acids and total

fats are consistently high in the blood of cancer patients and this increase is reduced by the roentgen rays. We do not care to give any reason or hypothesis for the reduction, as we are at present carrying on further studies along this line.

5 There is nothing in the behavior of the blood sugar or diastatic activity that is diagnostic of cancer. We have noted, however, that the roentgen rays activate the diastase for a short period of time to a greater than normal activity.

6 The plasma and corpuscle percentages were unaltered by the effect of the rays, and of no diagnostic value in cancer.

# THE CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS \*

JOSEPH EARLE MOORE, M D

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Since the introduction of the colloidal gold test of Lange,<sup>1</sup> numerous reports have appeared in the literature of examinations of the cerebrospinal fluid of large numbers of patients with neurologic diseases of all types

Characteristic results have been obtained only in neurosyphilis, and the findings of the various types of this disease are now well known. However, the so-called "paretic" gold curve, at first supposed to be pathognomonic of general paralysis, at least within the group of syphilitic disorders, has been obtained in a number of other conditions, among which are lead poisoning, tuberculous meningitis, brain tumor and multiple sclerosis. In the first three of these conditions the curve has not appeared with any regularity, but in the last named it seems to be more than an occasional finding. For this reason, it has been thought worth while to survey the material from this clinic and review the literature, with the object of determining if definite changes in the spinal fluid occur with any regularity in multiple sclerosis.

Textbooks on neurology make scant comment on this point. Such statements as do occur indicate nothing of a characteristic nature. Current literature is also lacking in definite information. In various reports of long series of neurologic and psychiatric cases in which the colloidal gold test has been employed on the spinal fluid, a few cases of multiple sclerosis appear, but the results obtained present no uniformity. Jaeger and Goldstein<sup>2</sup> report, in a few cases of multiple sclerosis (number not stated), a "slight" colloidal gold reaction, there being a faint color change in the first four or five tubes. Three of four cases reported by Eskuchen<sup>3</sup> were completely negative with the Wassermann and colloidal gold tests. The remaining case, which had been regarded as one of multiple sclerosis for years, was at once

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\* From the Department of Medicine and the Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital

1 Lange. *Berl klin Wchnschr* **49** 897, 1912, *Ztschr f Chemotherap*, **1** 44, 1913

2 Jaeger, R., and Goldstein, M. *Ztschr f d ges Neur u Psych* **23** 219, 1913

3 Eskuchen, K. *Ztschr f d ges Neur u Psych* **25** 486, 1914

diagnosed as cerebrospinal syphilis in spite of a negative Wassermann reaction in the blood and spinal fluid, because examination disclosed a pleocytosis, positive globulin and paretic colloidal gold curve in the fluid alone

Flesch<sup>4</sup> reports eight cases, one case completely negative, one case in which the colloidal gold test was slightly positive and other tests were negative, and six cases with the colloidal gold reaction of a paretic type, in which the precipitation was limited more strictly to the first few tubes than is the case in paresis. Kaplan<sup>5</sup> reports two cases, one serologically completely negative, the other with a paretic colloidal gold curve as the only positive finding. In a later paper,<sup>6</sup> reporting eighteen cases, seventeen were negative, and one gave complete precipitation of the gold in the first two tubes.

In this clinic, Miller and his co-workers<sup>7</sup> called attention to the presence of a paretic colloidal gold curve in the three cases of multiple sclerosis which they investigated. These cases are included in the present report.

Oetiker<sup>8</sup> reports two cases, one case with the globulin slightly positive and other findings negative, and one case in which there was no pleocytosis or globulin reaction, but the gold showed partial precipitation in the first five tubes, reaching as high as 3 plus. In Robertson's<sup>9</sup> case, the colloidal gold curve, instead of being paretic in type, showed a "verschieben nach oben," a reaction in the last tubes, reading 0000003355. Lowrey<sup>10</sup> reports one case with a paretic gold curve.

As regards pleocytosis, Rotstadt,<sup>11</sup> in an exhaustive article on the cells of the cerebrospinal fluid, states that in 75 per cent of his cases of multiple sclerosis (number not given) there was no pleocytosis.

These citations illustrate the status of the subject in the literature. It is obvious that nothing characteristic has been found so far. Of these forty cases, fourteen gave paretic gold curves, twenty-five were completely negative and one case was atypical. Because of the small number of cases reported and the lack of uniformity in the results obtained, it was thought worth while to examine the material from this clinic.

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4 Flesch, N. E. *Ztschr. f. d. ges. Neur. u. Psych.* **26** 318, 1914.

5 Kaplan, D. M. *J. A. M. A.* **62** 511 (Feb. 11) 1914.

6 Kaplan, D. M. *Ztschr. f. d. ges. Neur. u. Psych.*, **27** 246, 1915.

7 Miller, Brush, Hammers and Felton. *Bull. Johns Hopkins Hosp.* **26** 391, 1915.

8 Oetiker. *Ztschr. f. klin. med.* **82** 246 1916.

9 Robertson, W. E. *Boston M. & S. J.* **174** 136, 1916.

10 Lowrey. *J. Nerv. & Ment. Dis.* **46** 186 (Sept.) 1917.

11 Rotstadt, J. *Ztschr. f. d. ges. Neur. u. Psych.* **31** 228, 1916.



Since the introduction of the colloidal gold reaction, there have been in Johns Hopkins Hospital twenty-eight cases in which complete serologic examinations were made, and in which the clinical diagnosis was either certainly or probably multiple sclerosis. The results are presented in Table 1.

Examination of Table 1 reveals the fact that in sixteen cases there was a pleocytosis, considering any cell count larger than five to be abnormal. In twenty-five cases, globulin was detected, the amount being large in ten cases. Blood and spinal fluid Wassermanns were completely negative, except for one doubtful reaction with 10 cc of spinal fluid (which can be regarded as a nonspecific reaction). The gold curve was paretic in type eighteen times, syphilitic three times and negative seven times.

These figures become more striking when the validity of the clinical diagnosis is considered. It will be noted from Table 1 that the definite diagnosis of multiple sclerosis had been made without reserve twenty times before the laboratory examinations were made, and that it was questionable in the remaining eight cases, in which it was made solely as the best possibility. It is without the scope of this paper to discuss the clinical aspects of the disease. Suffice it to say that the diagnosis is often by no means made easily, and that in many cases, unless the patient is observed over long periods of time, it must remain in doubt. Taking these facts into consideration, Table 2 shows the number of cases in which pathologic findings occur in the two groups.

TABLE 2—SEROLOGIC FINDINGS IN TWO GROUPS OF CASES

Diagnosis	Number of Cases	Pleocytosis of More than 5 Cells	Globulin			Wassermann		Gold Curve			
			Strongly Positive	Positive	Negative	Positive	Negative	Paretic	Syphilitic	Atypical	Negative
Multiple sclerosis	20	8	9	9	2	0	20	18	0	0	2
Possible multiple sclerosis	8	8	1	6	1	0	8	0	3	0	5

Thus, in twenty cases of multiple sclerosis, a paretic gold curve, together with a positive globulin reaction, appeared in eighteen cases, or 90 per cent. This average is high enough to exclude the assumption of a merely occasional accidental finding of such a curve, and leads to the suspicion that in the other eight cases, diagnosed as being probably multiple sclerosis, the diagnosis is at fault, rather than the negative findings.

Excluding the rare cases of lead poisoning, tuberculous meningitis, etc., in which a paretic gold curve has occasionally been found, there are, therefore, only two diseases in which this type of curve occurs

with constancy, parenchymatous neurosyphilis and multiple sclerosis. There is usually no cause for confusion between these two, the diagnosis of neurosyphilis being in most cases clear enough from history, symptoms and clinical findings. If these fail to establish a definite diagnosis, one can fall back on the blood and spinal fluid Wassermann reactions. One or both of these will be positive in neurosyphilis, in fact, whenever a paretic gold curve is found in syphilis, the spinal fluid Wassermann is, so far as is known, always positive, with the single exception of long treated cases, in which the Wassermann becomes negative before the colloidal gold test.

As for the explanation of this reaction it is probably, as Felton<sup>12</sup> suggests, "an estimation of the albumin globulin content of the cerebrospinal fluid, rather than a specific reaction for any one lesion of the nervous system." This, of course, leaves unexplained why in neurosyphilis, multiple sclerosis and certain isolated cases of other nervous lesions, the albumin globulin content should be altered to the particular proportions necessary to produce a paretic gold curve.

#### SUMMARY

1 The cerebrospinal findings in twenty-eight cases of multiple sclerosis are reported.

2 In twenty of these cases the diagnosis is clinically certain, in the other eight cases it is clinically doubtful.

3 In the first group, the findings are (a) negative blood and spinal fluid Wassermann (all cases), (b) pleocytosis (eight cases), (c) positive globulin (eighteen cases), (d) paretic gold curve (eighteen cases). In the second group the findings are the same, except for the gold curve, which is syphilitic in three cases and negative in five cases.

4 Together with the clinical evidence, it is believed that the spinal fluid picture is fairly constant, and that, other things being equal, such a picture is a strong argument in favor of a diagnosis of multiple sclerosis. In its absence the diagnosis becomes at least doubtful.

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<sup>12</sup> Felton, L. D. Trans. A. M. A., Sect. Path. & Physiol., 1917, p. 73, Bull. Johns Hopkins Hosp. 30:242 (Aug. 1) 1919.

# CAVITY FORMATION AND ANNULAR PLEURAL SHADOWS IN PULMONARY TUBERCULOSIS

JAMES A HONEIJ, M D

NEW HAVEN, CONN

The signs of cavity in the lung, both on physical and roentgenologic examination, have always been a matter of interest and inquiry. The present paper aims to give added information on the subject, based, partly, on the examination and observation of a large number of cases in a tuberculosis hospital.

Some years ago my attention was drawn to shadows in roentgenograms suggesting cavities, although no physical signs of cavity formation were present, and for a considerable length of time the failure to substantiate by roentgenologic means cavity signs obtained on physical examination has been noted.

This inquiry covers cases with definite cavity formation and its classical signs, cases giving fair clinical evidence of cavity but not proven by roentgenologic methods, and cases giving certain roentgenologic images ranging from true cavity formation to simple pleural thickening, without clinical evidence.

## PATHOLOGY

Obviously, the reason for the more frequent occurrence of cavity formation near the apex, in the first and second costal interspaces, is that in the majority of cases the apex is the site of the oldest and most extensive lesions. Usually, where cavitation occurs other than in the region of the apex, the apex shows healed fibrous lesions, and below areas of more advanced and destructive processes without healing are present.

The pathology of tuberculosis is so well known that it is unnecessary to review it in detail. The outline given here is sufficient to appreciate more clearly the process of cavity formation. The process of infiltration, especially if localized, progressing into pneumonia-like areas with secondary pleural changes, or vice versa, should be borne in mind. It is a common experience to find the upper half to the upper third of the lung so firmly bound down by markedly thickened pleural adhesions (more so than at the base) that difficulty is incurred in removing the lung intact. These adhesions are often situated so close to the adherent surface of the lung that they are torn open when the organ is removed. Cavities occur more frequently at the anterior than at the posterior portion of the lung. Cavitation occurring nearer the central portion



of the lung is usually situated in the midst of an infiltrated area, and fibrous tissue plays no part in the outline of the cavity, unless the disease has been protracted, or unless there has been an attempt at healing. When cavitation takes place, the greater portion of one or both lungs is affected, unless there has been definite demarcation of the process by dense fibrous tissue as happens commonly at, or near, the interlobar fissure.

What has commonly been observed in the army hospital is the frequency of the hilus type of tuberculosis, that is, involvement of the middle portion of one lung, extending from the hilus region, secondary to advanced disease of the opposite lung. Cavitation under these conditions occurs just outside the hilus area. If tuberculosis involves both apices simultaneously, or nearly so, in time cavitation may occur subsequently at, or near, both apices. This, however, is not common unless the disease is extensive throughout both lungs.

It is always well to bear in mind that the greater the infiltration of the lung, both in density and extent, all else being equal, the more likely is cavitation to occur, the less the infiltration and the greater the fibrous tissue, the less likely is it that cavitation will occur.

Cavities occur because of softening and necrosis. The size of the cavity will depend on several factors, namely, on the extent of infiltrated or affected tissue, the size of the bronchus leading to the cavity, the amount of bronchial dilatation, the condition of the circulation in the immediate vicinity of the cavity, the position of the cavity where movement of the lung is not marked, whether occurring on the surface or margin, and on the resistance of the individual, or the amount of fibrous tissue produced.

The size and position of the cavity and the amount of pulmonary or pleural disease surrounding or covering it affect the diagnosis, provided other conditions (as will be taken up later) are taken into consideration. Recent cavities occurring in the rapid, acute cases have seldom a limiting membrane or lining, their walls are usually irregular and congested.

Cavities occurring in the chronic type of cases have, in most instances, a limiting fibrous membrane, the greater the resistance and chronicity of the case, the more markedly evident is the membrane or fibrous wall. These walls are usually covered with abundant thick pus but are themselves smooth and regular. The larger cavities are commonly traversed by fibrous bands, usually enclosing a blood vessel. Cavities of various sizes distinctly separated from each other may surround the larger cavity. The cavitation with irregular congested outline occurring in tuberculosis is closely simulated by the large abscess cavities which occur in nontuberculous cases. The largest cavities are most often found affecting the upper lobe, the interlobar thickening

forming a substantial lower wall or base to the cavity. Cavity formation may, of course, affect the whole lung, leaving only a very thin pleural sac containing abundant pus and often fluid.

Cavities may heal either through calcification or fibrous tissue formation. Healing depends, however, on the general systemic condition of the patient, the amount of resistance to infection, the stage of the disease, the character of the pulmonary changes, the position of the cavity and, particularly, on the size of the cavity. Cavities greater than 1 cm in diameter rarely heal. If healing takes place by calcification, the surrounding walls must contain a certain amount of normal tissue. The circulation must be normal, or at most only slightly impaired. Should healing take place by the formation of fibrous tissue, which is the more common reparation process, then the same conditions must be fulfilled. Under these circumstances the fibrous tissue may contract and obliterate the cavity, giving rise to an increased density of tissue. This evident density of tissue frequently may be diagnosed erroneously by the radiogram as infiltration. When healing takes place by the formation of fibrous tissue cavities may be separated completely from the surrounding tissue and cavities with smooth walls and outline may persist. This occurs most frequently in semichronic cases where healing and destruction of tissue take place alternately over a long period of time and where the cavities are situated near the pleural surface.

Thickening of the pleura, which occurs in the greater percentage of tuberculous cases, plays an important rôle in the size, shape and outline of cavities situated near the surface and in their healing and diagnosis.

#### REVIEW OF LITERATURE

Laennec's work and Kingston Fowler's study are not included as they are sufficiently well known. Ewart<sup>1</sup> gives the occurrence of cavities in the following ratio and position:

At the apices	282
In the dorsal axillary line	227
In the mammary region	189
In the sternal region	61
At the base	32

Allyn<sup>2</sup> states that cavities occur more frequently anteriorly, from the apex to the interspace. Foggie<sup>3</sup> reports a case of pulmonary tuber-

1 Ewart, W. Croonian Lectures, 1882.

2 Allyn, Herman B. The Diagnosis of Tuberculous Cavities in the Lung, *Am Med* 9 190, 1905.

3 Foggie, W. E. A Case of Pulmonary Tuberculosis with Whole Lung as One Cavity, *Edinburgh M J* 6 339, 1911.

culosis with the whole lung as one cavity and calls attention to the fact that it was erroneously diagnosed as a pneumothorax. In the same case the left lung also had a small cavity. The postmortem examination showed the lung surface covered with a thickened pleura which was densely adherent to the chest wall. Total destruction of the lung tissue resulted in the formation of a cavity in which a small amount of purulent material was present. Foggie also quotes cases cited by Louis in which three-fourths and four-fifths of the lung was destroyed. He also cites cases reported by Stokes and Ewart, in which there was loss of the whole lung, and twenty-five cases reported by West, in which the size of the cavity in every instance was not less than one half lobe.

Rieder<sup>4</sup> mentions the importance of determining the frequency of cavities, their location, size, changes in time (chronicity) and progress to other cavities, emphasizing the superiority of roentgenographic diagnosis over clinical diagnosis.

Mayer<sup>5</sup> draws attention to the difficulties of collapsing the lung when the cavities are high up in the apical region, and this obviously depends on the pleural adhesions between the lung and the thoracic wall.

Norris<sup>6</sup> calls attention to the obscurity of cavity signs which may be due to a thickened pleura. Cavities, he says, are more frequently overlooked than diagnosed as present when they are really absent. On the other hand, Mantoux<sup>7</sup> reports that in a number of cases of lung cavities, bacilli were difficult to demonstrate and concludes that in many cases in which tuberculous cavities exist a relatively small number of tubercle bacilli is present. Fishberg<sup>8</sup> considers that the acuteness and the duration of the process are two factors of importance in diagnosing tuberculous cavities. In chronic cases he calls attention to cavities with fibrous encapsulation and says that they always drain into a bronchus. As proof of this statement, he says that large numbers of bacilli are always found in the sputum. He also states that large cavities may shrink and that they are often obliterated by granulation tissue or by calcification. In his opinion, cavities may be an indication of the chronicity of the disease, which in my experience is not necessarily the case.

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4 Rieder, H. Kavernen bei Beginnender und bei Vorgeschrüttener Lungentuberkulose, Fortschr. a. d. Geb. d. Röntgenstrahlen **16** 1, 1910.

5 Mayer A. Die Behandlung der Kavernösen Phthise durch Extra- und Intrapleurale Pneumolyse, Deutsch. med. Wchnschr. **39** 2347, 1913.

6 Norris, George W. The Differential Diagnosis Between Incipient Pulmonary Tuberculosis, Healed Cavities and Non-Tuberculous Fibrosis, New York M. J. **80** 103, 1904.

7 Mantoux, C. Les Tuberculoses Cavitaires Paucibacillaires, Ann. de med. **5** 307, 1918.

8 Fishberg, Maurice. The Prognostic Significance of Tuberculous Cavities in the Lungs, New York M. J. **101** 1310, 1915.

Aimard<sup>9</sup> contributes an excellent report on silent cavities and false cavities. He emphasizes the fact that many cavities which occur in the full pulmonary field and are as large as a hen's egg, although seen roentgenographically, may never give physical signs. He quotes Gran-cher, who insists that certain conditions and their combinations must exist in order that a cavity be diagnosed by auscultation. The cavity must not be smaller than that of a small nut, it must contain a certain volume of air predominating over solids and liquids, the walls of the cavity must be covered by tissue that is dense and yet elastic enough to reflect the sounds, finally, the cavities must not be situated too deeply or be covered by bronchi. Aimard and also Tecon<sup>10</sup> believe that the left lung is affected more frequently than the right. They have reported 323 cases with cavities, on the left in 205 cases and on the right in 118 cases. The left apex is always affected. The left base is very rarely affected. On the right side, however, any portion of the lung may be affected with equal frequency. In every case the Koch bacillus was found in the sputum.

Lamy<sup>11</sup> reports the case of an aged adult with a cavity in each apex. This case is interesting, first, because of the marked involvement of the tracheobronchial glands, some of which had become partially softened, and, secondly, because death was the result of an acute laryngeal and tracheal attack following a marked tuberculous destruction of these structures.

In an article of unusual merit Pallasse and Roubier<sup>12</sup> review the question of tuberculous cavities at the base of the lung. This does not include cavitation of the base as an extension of the process from the apex downward, it includes only those cases where cavitation occurs first of all at the base, in the middle or lower part of the lower lobe, the process predominating there. These investigators quote the opinion of Laennec, Louis Walsche and Jaccoud regarding the rarity of base cavities. These authors hold that cavities of the base occupy exclusively the left base and are of occupational or pleural origin. Fagge believes that a tuberculous process never extends from the base upward and that tuberculosis of the base is better described as a chronic pneumonia. Percy-Kidd found in 412 consecutive necropsies only two cases of tuberculosis beginning at the base. Pallasse and Roubier also

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9 Aimard, J. Cavernes Muettes Tuberculeuses et Fausses Cavernes du Poumon, *Diagnostic Radiologique, J de Radiol et d'Electrol* 3 49, 1918

10 Tecon and Aimard. Gravité comparée des localisations tuberculeuses pulmonaires gauches et droites, *Etude de 2,000 cas, Rev med de la Suisse Rom* Janvier-Fevrier, 1916

11 Lamy. Ulcération Laryngo-Trachéo-Bronchique chez un Tuberculeux Cavitaire Mort a la Suite d'une Laryngo-Trachéite d'Evolution Aiguë, *Bull et mém Soc anat de Par* 87 149, 1912

12 Pallasse, E., and Roubier, C. Les Cavernes Tuberculeuses de la Base du Poumon, *Rev de la tuberc* 10 208, 1913

quote the opinions of Grancher, Rice and others on basal pneumonia processes in which cavity formation or abscesses occur. Obviously, there is no reason to consider such cases here. However, the only cases that are of interest from our point of view are those in which cavities occur in the usual fibrocaseous tuberculosis and in postpleuritic cavitation of the base. In Pallasse and Roubier's five cases the cavitation was found more posteriorly than anteriorly in four cases, in three cases, the walls of the cavity were densely sclerotic and the pulmonary tissue around the cavity showed marked sclerosis. The condition of the surrounding tissue and the presence of tubercles must be taken into consideration before a diagnosis of a tuberculous cavity is made.

Burnand and Tecon<sup>13</sup> believe that cavities occurring at the base are seldom cured. It is their opinion that cavities of the lower lobe most often follow tuberculous pleurisy with infiltration, although they result occasionally from a bacillary splenopneumonia which is undergoing necrosis. The latter sequence is sometimes seen in the progressive type of cases of common fibrocaseous tuberculosis. The authors also agree with other investigators that tuberculous cavitation of the base is not very common, only four cases occurring in the sanatorium. They quote the following figures from Meyer and Leysin. In 1900-1901, of 147 patients only four presented cavity formation at the base, in 1906-1907, of 118 patients only four cases showed a cavity at this point, and in 1907-1908, of 150 patients only three had a similar lesion. Well known anatomic and functional reasons are given to substantiate the opinion that cavities of the base are seldom cured.

Burnand<sup>14</sup> believes that cases of true closed pulmonary tuberculous cavities exist. These cavities are independent of the bronchi or air passages and have no connection with them. Under these circumstances cavitation occurs in the center of a focus, and at the same time stimulates sufficient connective tissue around it to enclose it thoroughly. Caseation and necrosis in the center progress with the thickening of production of connective tissue around the focus. Such conditions have already been referred to in connection with small cavities which frequently become cicatrized.

Walsh<sup>15</sup> reports a case of multiple lesions of both apices in which the cavitations closely resembled cysts. At necropsy these lobes proved to be tuberculous. From the description, the cavitation process probably originated in the pleura.

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13 Burnand, R. and Tecon, H. *Le Pronostic des Tuberculoses Cavitaires de la Base du Poumon*, *Rev. méd. de la Suisse Rom.* 30 511, 1910. Chahier, M. J. *Tuberculose Cavitaire de la Base, Greffée sur un Ancien Foyer de Bronchopneumonie, chez un Enfant d'un An et Demi*, *Lyon med.* 113-743, 1909.

14 Burnand, R. *Existe-t-il des Tuberculoses Pulmonaire Cavitaires Fermées?* *Rev. med. de la Suisse Rom.* 30 412, 1910.

15 Walsh, J. *Tuberculous Cavities Resembling Cysts at Apices of Lungs*, *Proc. Path. Soc., Phila.* 13 161 1910.

Cavities occurring in the lungs of children are of marked interest and have received a good deal of attention. In the opinion of Ribadeau-Dumas<sup>15</sup> they are more common than is supposed. He believes, with Barbier, that cavities are formed at the expense of the primary tuberculous nodule and that in this case, a fibrous capsule limits the caseous process. Cavities occurring in the lung represent confluent ulcerations appearing in a pneumonia area (Barbier) the walls of which are caseous, enclosed by fibrous tissue like the cavities in adults. Because of the difficulty of diagnosis Ribadeau-Dumas lays emphasis on the roentgenographic examination, as large cavities are invariably diagnosed by this method. Ribadeau-Dumas, Sauvan<sup>16</sup> and Pandolph<sup>17</sup> call attention to the habitual absence of physical signs.

Barbier,<sup>18</sup> in analyzing the frequency of cavity formation in pulmonary tuberculosis in infants, comes to some interesting conclusions. In 194 cases of pulmonary tuberculosis cavities were present in forty-eight cases giving in conjunction with the findings of other investigators, a proportion of twenty-nine per 100 tuberculous infants with cavity. Cavities occur more frequently between the ages of three and six months, but often are observed between six and eighteen months. Barbier asserts that the middle anterior part of the lung (that is the lower part of the upper lobe, or the upper part of the middle lobe) is most frequently attacked. Cavities the result of secondary foci however, attack the apex by preference and especially on the right side. Barbier, quoting Aine states that in fifty-two cases forty-four cavities occurred in a single lung and of these thirty-six were limited to a single lobe.

Lhomme<sup>19</sup> emphasizes the deceptive functional and physical signs of tuberculous cavities in infants. He mentions the work of Rilliet, Barthez and Cadet as pseudocavity sounds found in weak anemic tuberculous infants with temperature elevation. He emphasizes the lack of expectoration and the presence of hemoptysis in these cases and suggests that under these circumstances search should be made for tubercle bacilli in the feces. Lhomme quotes the following figures on the occurrence of hemoptysis: "Rilliet and Barthez do not find a single case of hemoptysis in individuals under 7 years of age. West

15a. Ribadeau-Dumas, L. Tuberculose Cavitaire du Premier Age. Bull. Soc. méd. de hôp. de Paris **36** 936 1913.

16. Sauvan, A. Caverne Tuberculeuse chez un Enfant de 13 Mois, Marseille méd. **64** 343, 1907.

17. Pandolph, B. M. Case of Cavitation of the Lung in an Infant Dying in the Seventh Month. Washington Med. Ann. **13** 149 1914.

18. Barbier, H. A propos de la Tuberculose Pulmonaire chez les Enfants de 0 à 2 Ans. Fréquence. Formes Cavitaires. Reactions Fibrineuses. Paris méd. **19** 169, 1917.

19. Lhomme, H. Cavernes Tuberculeuses chez les Nouveaux Nés. Pédiat. Internat. de la Tuberc. Paris **10** 401 1906.

found four cases, Powell, five cases, Carrie, six cases, Foss, seven cases, Cadet de Gassicourt, eight cases Henoch and Hendrick believe it is very rare in infants who have not reached the age of dentition Mantel found fourteen cases"

Weill recorded a tuberculous cavitation of the lower lobe of the left lung in an infant 18 months of age Enlarged caseated glands were in contact with the cavity A dorsal Pott's disease also was present in an infant 3 months of age Collet and Delachanal<sup>20</sup> found at necropsy a cavity involving the whole right upper lobe, and a smaller cavity in the upper part of the lower lobe Caseated tracheobronchial glands were present on the right side Pleural thickening with adhesions throughout the upper left lobe was demarcated

Delearde<sup>21</sup> reports a case of pulmonary cavity in an infant, 10 months of age There were no signs present which would indicate the very extensive lesions which were found at the necropsy The necropsy showed an area of caseous pneumonia extending to the middle lobe on the right, in the middle of which a cavity the size of a large nut and filled with caseous pus was found It is interesting to note, also, that the tracheobronchial glands formed a large mass contiguous with the pneumonic area

Bergman<sup>22</sup> in a postmortem made on an infant, found cavities in the upper part of the right lower lobe Similar cavities were present in the lower part of the left upper lobe These observations are interesting, for cavities occurred on both sides and in unusual positions The glands were also perceptibly enlarged

Buddy<sup>23</sup> reports an interesting case in an infant, 3 months old At the necropsy a cavity the size of a pigeon's egg was found at the root of the left lung, during life, physical signs persisted in this region Other smaller cavities were found along the vertebral border It is noteworthy that there was marked enlargement of the glands in chains, some glands at the root of the lung were caseated and had broken down Adhesive pleurisy was also found

#### ROENTGENOGRAPHIC FINDINGS

These will be taken up in the following order 1 Cavity 2 True annular shadows 3 Intrapulmonary annular shadows

1 *Cavity*—The basis for the study of cavities from a roentgenographic point of view rests on the postmortem findings and statistical

20 Collet and Delachanal Cavernes Tuberculeuses chez un Nourrisson de Trois Mois, Lyon med 115 317, 1910

21 Delearde Caverne Pulmonaire chez un Enfant de Dix Mois, Echo med du nord 9 606, 1905

22 Bergman, H Cavernose Lungentuberkulose beim Saugling, Berl klin Wchnschr 52 77, 1915

23 Buddy, E P Report of a Case of Pulmonary Tuberculosis with Cavity Formation in an Infant Aged Three Months, J Missouri M A 8 359, 1911

data The point regarding the pathology of cavitation emphasized in the first paper of this series applies, of course, here

Not all cavities are visible roentgenographically Size by itself is not important, small cavities, 2 cm in diameter, are frequently outlined more clearly, are more transparent and are more readily and correctly diagnosed than are larger cavities It is, therefore, necessary that cavities, irrespective of size, be in such a position that the greater number of factors in diagnosis play a part

Cavities at the apex usually show more clearly than those at the base, provided the cavities which are compared are similar in size, type, and so forth However, the fact must be borne in mind that there is less depth to the lung at the apex, and less degree of congestion and secretion with gravity to play a part Likewise, cavities occurring in or just outside the hilus area are more difficult to diagnose This is largely because of the depth of the lung In addition, the picture may be complicated by hilus shadows, congestion or fibrosis Very often the cavity may be overshadowed by the heart, while occasionally a localized emphysema may be present

Provided other factors are taken into account, cavities which occur in the full pulmonary field are detected more readily than in those parts of the lungs where the shadows and outlines might be confused with them Position, therefore, is of importance

The depth of the cavity—whether it occurs near or under the surface of the lung, or deep in the lung—is important If situated deep in the lung, then the size of the cavity is undoubtedly an important factor, but the important point is the exact position and size of the cavity in the lung

The contrast between cavity and lung tissue must be noteworthy, that is, the transparency in the area of cavitation must be greater than the normal transparency in that part of the lung, and, naturally, greater than that of the tissue surrounding it It is, therefore, important that close attention be paid to the tissue changes surrounding an area of transparency Usually, the greater the infiltration, or the more solid the lung, the greater the evidence that the area of transparency under observation, surrounded by this area of infiltration, is a cavity From the roentgenographic point of view this infiltration will show as a more or less irregular heavy density greater than the usual mottling If the density is more even and, perhaps, more opaque, then, in all probability, we are dealing with a pneumonia type of tuberculosis It is obvious that in speaking of cavity I have in mind the result of necrosis and softening in an infiltrated area Therefore, one should always bear in mind the pathology of different tuberculous processes when examining roentgenograms for possible cavitation



The duration of the disease indicates usually what may be expected besides the usual tuberculous changes, frequently repeated healing or breaking down may cause other tissue changes fibrosis, for instance, or if the surface of the lung is involved, pleural changes and in consequence, extra shadows and increased density with numerous outlines. Under these additional conditions the transparency of the suspected area will be lessened and its outline confused. The transparency of the cavity will vary just as much as the tissue density around it. This will depend (apart from the factors already mentioned) on the amount of air in the cavity. It must be in greater amount than the secretion or fluid present. The greater the amount of fluid present, the less likely will it be seen, and vice versa.

If the cavity is large and the secretion abundant, change of position of the patient from the prone to the upright posture will bring about a change in density or of fluid level. The lower portion of the cavity will then be denser than the upper portion and the upper outline will be clearer. The transparency of the area and the surrounding tissue density also may vary from week to week, may vary with inspiration and expiration as seen under the fluoroscope, and will, of course, vary if acute conditions are superimposed which will produce congestion and, perhaps, added secretion.

It is impossible to diagnose cavities when the density of the lung around the cavity (that is, back, front, or back and front of the cavity) is greater than the transparency. This is especially true if the cavity is small or filled with secretion.

The outline of cavities or areas suspected of being cavities is of diagnostic importance, but only after the above points have been considered. Cavities may have a clear cut, sharply demarcated outline, clearly differentiated from the surrounding tissue, or they may have an irregular, obscure outline that fades into the surrounding lung substance. The first condition usually indicates a fibrous wall, the second, cavity with continued destruction of lung tissue without definite walls or fibrous tissue outline. The first type of cavity is usually chronic, although the reaction of the lung tissue may be quite marked in acute self-limiting cases. In those cavities with a fibrous wall one can also invariably find shadows indicating fibrous tissue elsewhere in the lung (Table 1). Under these circumstances one must particularly take into consideration the shadows produced by thickened pleura, the outline of which may be confused with the fibrous wall outline of a cavity or cavities. This is especially true if the outlines of several cavities are superimposed one on another. These cases are most often easy of diagnosis, provided one can definitely eliminate shadows produced by the pleura. This point will be taken up later.

TABLE 1—ROENTGENOGRAPHIC FINDINGS IN CASES WITH CAVITY

No	Tuberculosis			Thorax		Rib Spaces		Angle		Cavity Position	Shape	Size in Cm	Outline	Transparent	Semiopaque	Opaque	Fibrous Bands	Fibrous Outline	Infiltration	Mottling	Calcification	Anterior Posterior
	Right	Left	Advanced	Moderate	Incipient	Sym Asym	Long Broad	Narrow	Wide													
21 6D	Adv rt, ? lt		+			Asym	L SI B +	+	+	Left apex, ? rt Minute sponge like annular shadows throughout right upper and middle 1st rib up, left 2d rib up, rt 3d rib up, lt	Circ All oval	5×4½ Average from 2 to 3 mm 5½×5½ 3 cm +	Reg Sharp	+	+		+	SI	+	++		AP AP
711 170	R		+			Asym	Long +	+	+	1st rib up, left 2d rib up, rt 3d rib up, lt	Circ Oval and circ	2 cm and more 1 cm + Indef Indef 1 cm and more 5×5	Sharp Def	++		Light	SI	+	++	++		AP AP
16G	R-L		R	L			+	+	+	Several rt and lt, 2d space up	Oval and circ	2 cm and more 1 cm + Indef Indef 1 cm and more 5×5	Indef and sharp Indef Indef Indef		+	+	+	SI	+	+		AP
707 71A 84B	R-L R-L R-L		R + R	I L		Asym	I ong Long	+	+	3d rib up, mult Apices Multiple, 3d rib up	Ind Ind	2 cm and more 2½×2½	Indef Dull	++	+		Indef	Indef	++	++		AP AP
123S	R-L		+			+		+	+	3d rib to 1st rib	Irr oval Ind	2 cm and more 2½×2½	Dull	+	+		+	+	SI	+		+
127S	R-L		+			+		+	+	Multiple, rt apex above 1st rib 2d rib up, rt 1st to 3d rib, lt 3d rib up, rt mul 3d rib up, lt mul multiple, 1st rib up, lt 3d rib up, rt Left apex	Oval	2 cm and more 2½×2½	Dull	++	+		++	++	SI	+		AP
197M 199G 150G	R-L R-L R-L		R L +	L R		Asym	I ong Long	+	+	3d rib up, lt mul multiple, 1st rib up, lt 3d rib up, rt Left apex	Irr	3 cm +	Sharp reg	++	+		++	++	++	++		AP AP AP
1707 178S			+			Asym	I ong I ong	R	L +	1st space, lt	Ind Circ	Indef 6×6	Indef Reg, def	++	+		SI	Indef	+	+		AP AP
201T	R-L		+				+	+	+	1st space, lt	Irr oval	6-2.3 1½ right, 1 1½ 2 left	Sharp, Irreg right, dull, Irreg left	+	+		+	+	+	+		+
225U	R-L		+				L-B	+	+	Sever 1st and 2d spaces, rt and lt	Circ	2 to 3 and more 3×3, rt 5+, lt	Sharp	L	R		+	+	L	RI		+
276O	R-L		Pneumothorax + right				I ong	+	+	Multiple, 1st, 2d 3d spaces, rt	Circ and oval	2 to 3 and more 3×3, rt 5+, lt	Sharp	+			+		+	+		AP
277C			+			Sym	Broad	R	I	Over 1st rib rt 2d rib up lt	Circ oval	1 cm and more 1×1½, and more	Indef						+	+		AP
277D	R-L		L		R		+	+	+	Sever 1st and 2d spaces, rt and lt	Circ oval	1 cm and more 1×1½, and more	Dull	+					+	+		AP
278Y	R-L		+			+		+	+	Upper left mult	Circ oval	1 cm and more 1×1½, and more	Dull		+				+	+		+

TABLE 1 — ROENTGENOGRAPHIC FINDINGS IN CASLS WITH CAVITY—(Continued)

No.	Tuberculosis				Thorax		Rib Spaces		Angle		Cavity Position	Shape	Size in Cm	Outline	Transparent	Semiopaque	Opaque	Fibrous Bands	Fibrous Outline	Infiltration	Mottling	Calcification	Anterior Posterior
	Right-Left	Advanced	Moderate	Incl.vent	Symm Asym	Long Broad	Narrow	Wide	Right	Gradual	Acute												
800D	R-L	R	I		Asym	Long Broad			R	R		Circ Ind Oval	10×9 Indef 4×5	Sharp Indef Reg, dull	+	+		+	IS	+	+	+	+
800B			R		Asym				R	L		Circ and oval	2 cm +	Indef	+	+		IS	IS	+	+	+	+
808O					Long							Circ and oval	3 cm +	Def and ind	+			IS	IS	+	+	+	+
812W		Pneumothorax left				I B						Circ and oval	3 cm +	Def and ind	+			IS	IS	+	+	+	+
813Y	R-L		+		Asym	SI			+			Irr	3×3½	Indef	+			+	IS	+	+	+	+
866U							Nar, Sh		+			Circ	3×3	Irr	+			+	IS	+	+	+	+
877E	R-L	R	I			I						Circ and oval	5×4 3×4	Sharp	+			+	+	+	+	+	+
813L	R		+			L B				+		Circ	3½×3½ 2½×2	SI irreg	1st	2d		SI	SI	+	+	+	+
810J	R-L											Ob	2×1½ 3×4	Dull	+	+		SI	SI	+	+	+	+
850S	R-L					+			+			Circ	1½×1½ 2 cm +	Dull	+	+		SI	SI	+	+	+	+
861M	R-L					+			+			Irr	6×6 6×4	Dull	+	+		SI	SI	+	+	+	+
862W	R-L					+			+		+	Oval	6×6 6×4	Dull	+	+		+	+	+	+	+	+
818Q					Asym L	L B				+		Circ	6×6½	Indef		+		+	+	+	+	+	+
815H					Symm R	Broad				+		Oval	6×4 5×4, lt	Reg, rt Dull, lt	R	L		+	+	+	+	+	+
810A	R-L					+			R	L		Circ and oval	2 cm + 3×2	Dull and sharp		+		+	+	+	+	+	+
852K	R-L					+	Normal				+	Circ	4½×1	Dull	+	+		+	+	+	+	+	+
850Q	R-L				Asym R	Long	Normal		L	R		Circ	2×1 Indef 1 cm +	Sharp Indef	+	+		+	+	+	+	+	+
857M												Ind	Indef	Indef	+	+		SI	Indef	+	+	+	+
888D					Long							Circ	3×3	Sharp, reg	+	+		+	+	+	+	+	+
705B		L ap			Symm	Long			+			Circ	3×3	Sharp, reg	+	+		+	+	+	+	+	+
707N		L	R			L B			+	+		Circ	4×4 1 cm +	Sharp, reg	+	+		+	+	+	+	+	+
715M					Broad				+	+		Circ	1 cm +	Reg	+	+		+	+	+	+	+	+

722S	R L	+		+		+		+		Both upper lobes	Many oval and circ, 2 em rt	5x7 rt 5x3 lt 3x3 1/2 lt 3x1 1/4 lt	Dull	L	R	R & L	SI	+	+	-	\ P
760D		+								Multiple, lt 3d rib up	Ind	2 em +	Indef				SI	+	+	-	\ P
768C		R								Multiple, right apex	Ind	1 em, + 3 em +	Indef		+	SI	SI	SI	+	-	A-P
769F	R L	+								Right, all lobes, left, 2d rib up	Oval circ.	3 em +	Reg, sharp	+		+	+	+	+	-	\ P
780B		+								2d rib up, both sides	Circ	4x4 +	Indef	L	R	+	Undet	+	+	-	A-P
811L		+								Multiple, 2d rib up, left, 3d rib up, right	Circ	2 em +	Def	+		+	SI	+	+	-	\ P
810S		+								Multiple, 3d rib up, both sides	Circ oval	3 em +	Def	+		SI	SI	+	+	-	A-P
830A		+								Right apex	SI	2x1 5	Reg	+		SI	SI	+	+	-	A-P
848T		+								Multiple, right 3d rib up	Indef oval	Indef	Indef	+	+	-	-	+	+	-	A-P
853M		+								Multiple, left 3d rib up	Ind	1 em +	Indef	+	+	Indef	Indef	+	+	-	Indef
895C		+								Multiple, 3d rib up left	Ind	1 em +	Indef	+	+	-	+	SI	+	-	\ P
930D		+								Over 3d rib, rt 3d rib up, lt, multiple	Ind	Indef	Indef	+		+	SI	+	+	-	\ P
936L		L								1st space, left	Circ	3 5x3	Reg, sharp	+	+	+	+	SI	+	-	Undet A-P
951G		+								5th rib up, right, multiple	Circ	4 em +	Reg, sharp	+	+	+	+	+	+	-	A-P
960V		+								3d rib up, left	Circ	5 em +	Reg, sharp	+	+	+	+	+	+	-	A-P
975O		+								3d to 1st rib, lt	Oval	4x6 3x2	Reg, dull	+	+	+	+	+	+	-	A-P
981W		+								Multiple, 2d rib up, both sides	Ind	Indef	Indef	+		+	-	+	+	-	A-P
991F										1st space and apex left (?)	Circ	2 em +	Def, reg	+			SI	+	+	-	+
1002T										4th rib up, rt, multiple	Ind	Indef	Indef	+	+		?	-	+	-	A-P
1004O										1st space, right, 3d rib up left	Circ	2-6 em	Reg, dull		+			+	+	-	\ P
1030L		+								2d rib up, left	Circ	3 em +	Reg, dull		+	SI	SI	+	+	-	A-P
1086S		+								Multiple, both sides	Ind	Indef	Indef			+	-	+	+	-	\ P
1112M		L								? Apices	Circ	1 em +	Indef	+		+	+	+	+	-	?
1163I										3d rib up, lt, multiple	Ind	Indef	Indef			+	+	+	+	-	A-P
1169P		R								2d rib up, right	Circ	8 5x8	Irr	+		+	+	+	+	-	A-P
1170O		+								2d rib up, both sides	Circ	6x7 rt 2x1 5 lt 3 5x4	Dull, irreg	L	R	+	+	+	+	-	\ P
1181H										1st space and apex, right	Circ	3 5x4	Def, reg	+		+	+	+	+	-	A-P
1185O		R								1st rib and 1st space right	Circ	4x4 5x5 5	Reg, dull	+		+	+	+	+	-	Undet

\* More pleural than parenchyma

TABLE 2—SUMMARY OF THE ROENTGENOGRAPHIC FINDINGS IN SEVENTY-FOUR CASES OF TUBERCULOSIS WITH CAVITATION RECORDED IN TABLE 1

Stage of the Disease—		Cases		Position of Cavity—		Right Left		Both Sides	
Advanced tuberculosis of both sides		45		5th rib and above		1			
Advanced tuberculosis of right side only		1		4th rib and above		3			
Advanced tuberculosis of left side only		1		3d space above		1			
Advanced tuberculosis, right, moderate				3d rib and above		8	15	6	
tuberculosis left		11		2d space above		1	2	3	
Advanced tuberculosis, left, moderate				2d rib and above		10	6	6	
tuberculosis right		6		1st space above		4	7	2	
Advanced tuberculosis, right, question				1st rib and above		8	5	1	
able tuberculosis, left		1		Apex		1		1	
Advanced tuberculosis, left, incipient				All lobes		1		1	
tuberculosis right		1		Middle and lower lobes		1			
Moderate tuberculosis of both sides		5		Upper and middle lobes		1			
Moderate tuberculosis of right side only		1							
Moderate tuberculosis, right, incipient									
tuberculosis, left		1							
Moderate tuberculosis, left, incipient									
tuberculosis right		1							
Total		74		Size of Cavity—				Cases	
				Greatest diameter over 5 cm				22	
				Greatest diameter over 4 cm				9	
				Greatest diameter over 3 cm				20	
				Greatest diameter less than 3 cm				32	
				Multiple, indefinite				13	
Shape of Thorax—		Cases		Shape of Cavity—				Cases	
Broad		25		Circular				42	
Slightly broad		1		Oval				26	
Long		31		Oblong				1	
Broad and long		17		Indefinite				22	
Total		74		Outline of Cavity—				Cases	
Rib Spaces and Angle of Ribs—		Cases		Regular				20	
Wide rib space and right angle		14		Irregular				6	
Wide rib space, gradual angle (20-71)		21		Sharp				29	
Wide rib space and acute angle		6		Dull				21	
Wide rib space, angle not given		1		Indefinite				24	
Narrow rib space and right angle		8		Transparency—				Cases	
Narrow rib space and gradual angle		7		Transparent				48	
Narrow rib space and acute angle		2		Semiopaque				32	
Narrow, right, wide, left, right angle		3		Indefinite				1	
Narrow, left, wide, right, right angle		1							
Narrow, left wide right, right angle		1							
right, gradual left		1							
Narrow, left wide, right gradual angle		1							
Normal rib space and acute angle		1							
Wide rib space, right angle, left grad									
ual, right		3							
Wide rib space right angle right, grad									
ual, left		2							
Rib space not given gradual angle		1							
Not given		2							
Total		74							

The lung changes usually indicate whether the diagnosis of the second type of cavity is warranted or not. If there is surrounding infiltration, if the case is progressive, if there is absence of fibrous tissue, and if all other conditions are equal, the area of transparency with ragged, irregular outline can be diagnosed as a cavity. This cavity will in all probability either grow larger or other areas will in time be seen, behind, in front of, or on either side of it.

The shape of cavities aids in the diagnosis. Circular or oval areas, even and regular in outline predominate in the majority of cases. A true cavity, especially one with fibrous wall, is seldom anything but oval or circular. In cases where cavity outlines are superimposed one over the other care should be taken that the resulting irregular outlines are not confused with the regular outline of a single cavity. Likewise, outlines of the rib, the border of the scapula or of the mediastinum,

bronchial markings, or bands from a thickened pleura may be confused with the outline of the cavity

Lastly, the unilateral asymmetry of the thorax must be taken into consideration, contraction of the rib spaces, the increased angle of the ribs themselves from the spine, and the narrow bony apical outline, as well as the total narrowness of the thorax, in short, any appear-



Fig 1—Case 71 Roentgenogram of lungs in a fairly early case. There is typical pleural thickening on the right side with annular shadow, not circular. This roentgenogram demonstrates a stage in the development of pleural annular shadows.

ance of the thorax to indicate lack of respiratory effort or lack of lung function, and, therefore, immobilization of the chest wall, especially if in contrast to the opposite side. If there is cavitation at the apex, it is surprising to see the degree of contraction or collapse that takes

place in the thorax wall from the apex to the third or fourth ribs. The physical findings should be included in all cases of cavitation, especially when the roentgenogram fails to give complete or definite evidence.

*2 True Annular Shadows*—These shadows are produced by the pleura. They have no relation to pulmonary infiltration or softening.



Fig 2—Case 225. Roentgenogram of the lungs in an advanced case with large multiple cavitation, not typical and in earlier stages more difficult to diagnose.

and breaking down of lung tissue. It is true that the two conditions may coexist, but it is equally true that pleural changes may be secondary to cavitation, or vice versa. Consequently, if a case is presented in which cavitation is accompanied by a pleural annular shadow, it is generally impossible to differentiate the two conditions (Case 1

TABLE 3—PLEURAL AND BRONCHIAL ANNULAR SHADOWS

Number	Date	Position	Size	Type
1094 O	4/25/19	1st rib, left	3.5 × 2.5	Intrapulmonary Br
733 D	1/27/19	3d rib up, right	Multiple, indistinct	Intrapulmonary Br
901 M	4/17/19	2d rib up, right	3 × 3	Intrapulmonary Br
966 B	3/ 5/19	2d to 1st rib, left	3.5 × 3	Intrapulmonary Br
71 A	7/ 8/18	4th to 2d rib, right	7 × 5	Pleural
687 M	12/ 6/18	Over 2d rib, right	4 × 2.5	Pleural
1137 J	4/30/19	2d rib to apex, right	Indefinite, several circles, 2+ cm.	Intrapulmonary Br
1127 P	4/28/19	Left apex	3 × 3, indistinct	Intrapulmonary Br
994 M	3/13/19	Over 1st rib, right	3 × 2.5	Pleural
993 F	3/19/19	1st space, left	2 × 1.5, indistinct	Intrapulmonary Br
	and	Over 3d rib, left	3.5 × 3, full field	
	5/ 8/19	Over 4th rib, right	4 × 3	Pleural or intrapulmonary Br
986 L	3/ 8/19	Over 1st rib, left	3 × 3	?Pleural
479 W	2/17/19	Over 2d rib, left	4 × 3	Pleural
	and			
	4/29/19	Over 2d rib, left	4 × 4	?Intrapulmonary Br
1096 B	4/25/19	2d to 1st rib, right	5 × 4, indistinct	?Intrapulmonary Br
1091 R	4/25/19	2d to 1st rib, right	4 × 4, indistinct	Intrapulmonary Br
1129 D	5/ 1/19	Over 1st rib, left	4 × 4, sl indistinct	Intrapulmonary Br
1140 V	4/30/19	3d rib up, left, 2d rib up, right	Multiple small and large circles, diffuse outline	?Cavitation and annular, pleural
455 W	3/14/19	3d space, right	3 × 1.5	Pleural
656 G	11/30/18	2d space, left	Several overlapping 2 × 2 and 1 × 1	Intrapulmonary Br
1144 H	4/30/19	Apex, left	2.5 × 1.5	Intrapulmonary Br
832 M	3/19/19	Over 1st rib, left, outer	5 × 4	Intrapulmonary Br
853 S	3/27/19	1st to 3d rib from hilus, right	5 × 5	Intrapulmonary Br
828 B	3/ 8/19	2d rib to apex, left	5.5 × 4	Pleural
1009 M	4/13/19	Apex, left	3 × 3	Intrapulmonary Br
		Apex, right	3 × 3	
663 F	2/17/19	3d to 2d rib, left	2.5 × 2.5	Intrapulmonary Br
		3d to 1st rib, right	4 × 4 × 4 (triangle)	
983 D	3/11/19	2d rib, right and left	Several superimposed 2+ cm	?Intrapulmonary Br and pleural
B	4/28/19	2d rib to apex, right	Irregular, double circle	Intrapulmonary Br
1128 K	4/28/19	Over 1st rib, left	3 × 3	Pleural
1181 H	5/ 7/19	Over 3d rib, left, cavity right apex	2.5 × 4	Intrapulmonary Br
1174 B	5/ 6/19	1st rib, left	3 × 3	Pleural
466 U	5/ 9/19	2d and 3d ribs, right, cavity left apex	4 × 4 and 3 × 3	Pleural and intrapulmonary Br
369 M	9/ 4/18	2d space, right	1.5 × 1.5	Pleural
661 D	12/7 and 11/18/18*	4th space, left	5 × 5	Pleural
119 F	3/17/19	2d rib and 1st space, right	5 × 5	Intrapulmonary Br and pleural

\* 4th of April and 7th of May, no trace No emphysema at any time

TABLE 4—SUMMARY OF FINDINGS SHOWN IN TABLE 3

Position—	Left	Right	Size—	Cases
4th space	1		Over 5 cm in greatest diameter	8
4th rib and up	1	1	Over 4 cm in greatest diameter	8
3d space		1	Over 3 cm in greatest diameter	13
3d rib and up	4	4	Less than 3 cm in greatest diameter	4
2d space	1	1	Multiple, indefinite	6
2d rib and up	5	9		
1st rib and up	6	1		
Apex	3	1		
Type—	Cases	Type—	Cases	
Intrapulmonary bronchial	17	Ques pleural	2	
Ques intrapulmonary bronchial	2	Intrapulmonary Br and pleural	2	
Pleural	10	Ques intrapulmonary Br and pleural	2	



390 D) Under these circumstances it appears that the process of cavitation in the lung is anchored for beneficial purposes by the pleura

CASE 1 (390 D) — Examined Feb 17, 1919 A definite annular shadow found in the right upper lobe accompanied by pleural thickening No evidence of cavitation Examined again May 19, 1919 Stereoscopic roentgenograms gave an unusual picture of positive cavitation in the right upper lobe, demarcated sharply below by the interlobar fissure, which was seen as a heavy opaque band Above this band the transparency was marked with great depth and no lung markings There was absolutely no positive physical signs of cavitation present

An annular shadow, in most cases, is larger than a true cavity, being generally four or more centimeters in diameter Consequently, a large size is in favor of its being pleural These shadows are by no means as common in the apical region as are those of cavitation Table 3 demonstrates this These annular shadows are more superficial They appear to be nearer the surface and usually seem to be on an even plane

The inner and outer borders of the outline of an annular shadow usually differ more than do those of cavities The inner border is usually sharply demarcated and smooth, as is found in a cavity with a well formed fibrous wall The outer border fades off, is usually not demarcated from the surrounding tissue and so differs from the sharp inner border The transparency of an area within a ring, in a slightly affected lung is, of course, no greater than any other part of the lung There is also no reason why in an affected lung, say infiltrated, a true annular shadow should give an inner area of transparency In cases where the annular shadow and lung cavitation combine, the case is different

Annular shadows are not necessarily of a regular oval or circular outline The contour depends on the position of the shadow, the duration of the pleurisy and on other physical facts They are much less liable to be circular than are the majority of cavities Not infrequently, three-fourths of the circumference of annular shadows is regularly circular, the remaining one-fourth being irregular with an indefinite border This is more likely to be the case when the pleurisy is extensive Under the latter circumstances the diagnosis of an annular shadow is usually easier, and also the fewer lung changes there are, the easier the diagnosis of the presence of annular shadows

Annular shadows are the result of adhesions between the parietal and parenchymal pleural surfaces subsequent to inflammation Under certain conditions there is an oval or circular arrangement of the pleura to the formation of which the movement of the lung and thorax contributes, resulting in the formation of a central or local pseudo-emphysema The area around the annular shadow which borders on the shadow represents the more firmly attached or organized pleura In

an interesting case of a light cortical pneumonia, observed early at the army hospital, a distinct annular shadow over the fourth space in front and in the full pulmonary field was noted. The shadow was at first localized and even but progressively developed into an annular type which later gradually disappeared. The whole process developed during a period of four months and has proved to be tuberculous in origin. The clinical observations agreed with the roentgenographic findings.



Fig 3—Case 707. Roentgenogram of the lungs in an advanced, rapidly progressing case. The atypical annular shadow is more difficult to diagnose. Probably early multiple cavitation was present. Frequent reexamination is important in these cases.

The most important question in the majority of cases is whether the lung condition warrants a diagnosis of tuberculosis. If this is established, then one must determine whether the disease is sufficiently advanced to make the diagnosis of cavity probable. Consequently, the appearance of annular shadows in such cases must have a relation to

the underlying lung condition (Case 1 390 D) If physical signs are insufficient to establish the diagnosis of cavity, the assumption is warranted that the annular shadow is due to pleural inflammation From the foregoing it may appear that it is a simple matter to differentiate accurately between cavitation and annular shadows, yet this is not the case Size, position, lack of transparency, gradual fading of the outer border, evidence of pleurisy, absence of advanced pulmonary changes, and so forth, are aids in differential diagnosis but nothing more

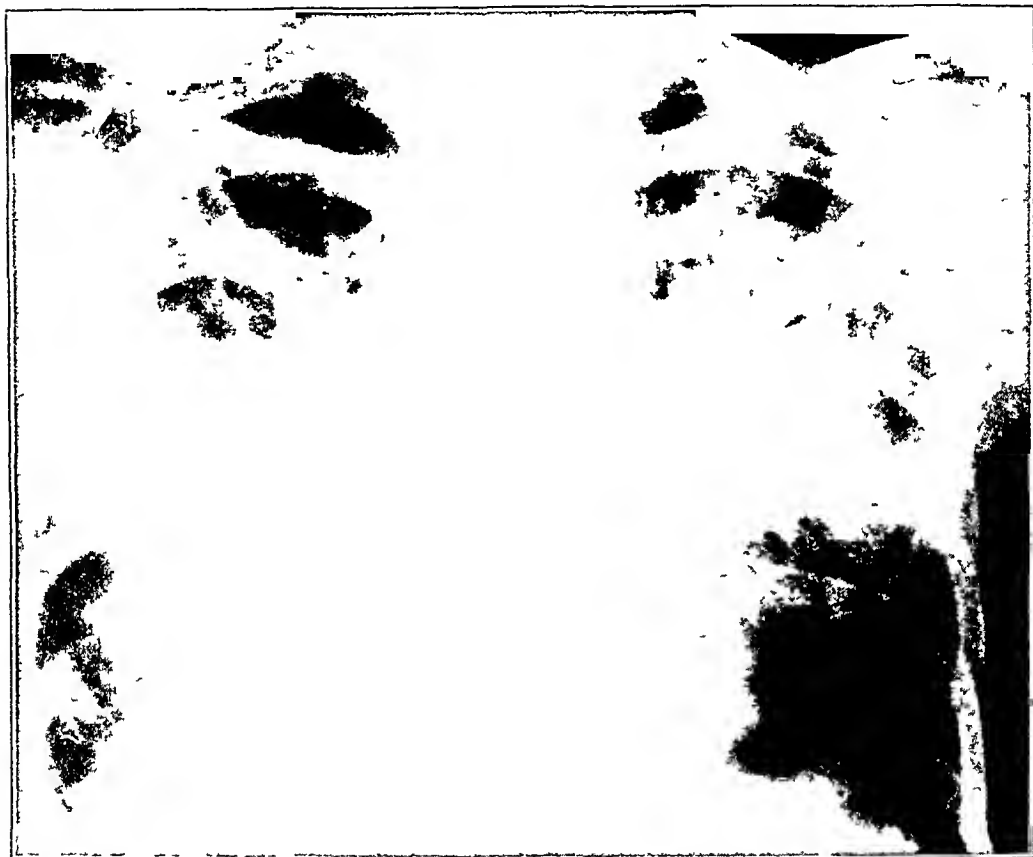


FIG 4—Case 811 Roentgenogram of the lungs in an advanced bilateral case showing the presence of a large typical cavity in the right lung and multiple cavitation throughout both lungs

Just as physical signs disappear in ordinary clinical cases of pleurisy, so in the course of a few months annular shadows also may appear (Case 2 768 C) The absence of progressive lung changes in the face of modification in the shadows is added proof that the latter are pleural in origin

CASE 2 (768 C) —Examined Feb 25, 1919, and a distinct annular shadow was seen at the second interspace on the left May 19 the patient was reexamined and no evidence of annular shadow was found The local lung density had not increased although some advance of the disease was seen in both lungs

3 *Intrapulmonary Annular Shadows*—In a small percentage of cases these shadows occur in the full pulmonary field. Invariably, they are just outside the hilus area, one border of the ring shading off into the hilus itself. Although very rarely mistaken for cavities, these shadows may easily be confused with pleural annular shadows. Intrapulmonary annular shadows are rarely as regularly oval or circular as true annular shadows. Their walls commonly resemble peribronchial thickening and in the majority of cases a well defined communication is seen between the shadow and bronchi at the hilus or in the full pulmonary field. The inner border of the shadow does not differ from the outer, both are slightly irregular or fuzzy in outline. The transparency of the inner area is no greater than that of other portions of the lung. These shadows can invariably be diagnosed. If closely examined with the stereoscope, it will be found that the medial portion of the shadow, that is, the portion resting on the hilus, is heavier than the distal portion, and that it is definitely bronchial and hilic in origin. The distal portion fades off, and ordinarily the two points which form an arc or the outer half of the annular shadow, are separated.

The stereoscope definitely indicates that intrapulmonary annular shadows are formed by two or more bronchial or root branches, and that they are neither pleural nor cortical in origin. These intrapulmonary shadows are seldom seen either in the second or in the advanced stage of tuberculosis. Indeed, if tuberculosis is present to any marked degree, these shadows are made out with difficulty. They are due to definite fibrous peribronchial changes and do not disappear. With the exception of aiding in ruling out tuberculosis, clinical evidence seldom assists in the diagnosis. A very unusual example of this type of shadow is illustrated in Case 3, 853 S.

#### SUMMARY

To summarize. There are three conditions which at times may be confused and which make a differential diagnosis difficult or often impossible. These include (a) true cavitation in pulmonary tuberculosis, with and without fibrous walls, (b) true pleural annular shadows, with and without pulmonary disease, (c) false annular shadows of intrapulmonary bronchial origin, occurring in early pulmonary tuberculosis and other chest conditions. These three conditions are illustrated here.

I have shown that a clear understanding of the pathologic processes involved, thorough appreciation of the different clinical signs is needed, and since, in a broad sense, we are less interested in the presence or absence of cavitation than in its affect on diagnosis, treatment and prognosis, it is essential carefully to consider other acute or chronic lung lesions in conjunction with the direct evidence of cavitation.

Apical pleural adhesions are, of course, of much greater weight in the diagnosis of pulmonary lymphatic tuberculosis than are similar changes at the base. However, the mere presence of an apical annular shadow, although it may be due to the same process which occurs frequently at the base, invariably leads to a more serious diagnosis than is warranted. If the movement of the lung at the apex were as great as at the base (all other conditions being equal), probably fewer annular shadows would result from pleural thickening. If tuberculosis of the base of the lung occurred more frequently, we would be led, in a large number of cases, to a different diagnosis than that of mere



Fig 5—Case 828 Roentgenogram of the lungs in an advanced case, showing a large, very typical cavity in the left apex with smaller multiple cavities in the right apex.

pleural thickening. On the other hand, if every annular shadow depended on a cavitation in the lung, then the frequency of lung cavitation would be increased enormously. Under these circumstances the presence or absence of preceding infiltration is unessential.

In many cases distinctly oval or circular areas of transparency which confuse the diagnosis are found. These areas, which are often outlined by bronchial shadows, bony structures, or most frequently by

the hilus, may be mistaken for cavitation, annular shadows or even bronchiectasis, occasionally they are produced by a localized emphysema (Case 119 F and Case 1131 M ) Finally, the physics of roentgenology and the limitations in roentgenologic diagnosis must be remembered If acute, congestive conditions prevail, it may be impossible to differentiate the lesions mentioned Repeated roentgenological and physical examinations are, therefore, clearly indicated



Fig 6—Case 840 Roentgenograms of the lungs in a case demonstrating the difficulty often encountered in making a diagnosis of cavity and annular shadow

#### CLINICAL FEATURES

The difficulty in determining the presence of a cavity can readily be imagined by a study of the pathologic and roentgenologic findings in this condition The roentgenologist errs more frequently in failing to diagnose a lesion when it is present than in diagnosing cavitation when it does not exist Clinically, the reverse is true A diagnosis of

cavitation is frequently made when no cavity is present. This is no reflection on the clinician, for in both physical and roentgenologic diagnosis there are similar limitations. To illustrate this point the following cases are presented.

CASE 3 (1021 P) — Clinically, this was an advanced case of pulmonary tuberculosis. On physical examination, there were definite signs of cavity, such as whispered pectoriloquy and bronchial breathing. There was an area of hyperresonance on percussion localized over the upper lobe of the right lung. On roentgenologic examination, the right lung was markedly consolidated without evidence of cavitation. Postmortem examination demonstrated the correctness of the roentgenologic findings. It is well known clinically that fluid and consolidation may give some of the signs of cavitation. It is equally well known that large cavities may exist without physical signs.

CASE 4 (390 D) — Clinically this was a case of active pulmonary tuberculosis involving the upper and middle lobes of the right lung and the upper and lower lobes of the left lung. Roentgenograms made September, 1918, and February, 1919, confirmed the clinical diagnosis. A third roentgenographic examination at the end of April, 1919, showed a definite cavity involving the whole upper lobe sharply demarcated by thickened fibrous tissue and interlobar pleura. Clinically, positive signs of a cavity could not be decided until June.

In briefly reviewing some of the literature several points of interest are brought out. Aimard<sup>9</sup> calls attention to so-called "silent" cavities. However, it is not clear whether or not he includes under this heading annular pleural shadows that are not cavities. He divides cavities into three classes, under the third class, he places those in which the contours are effaced, indicating an arresting of the process. These manifest no clinical signs of cavity and their outlines may disappear. "Again," he states, "one sometimes encounters false silent cavities which might be taken for real ones. These are chiefly seated at the right apex."

Paillard and Robert<sup>24</sup> summarize very well the physical findings in cavitation. In large cavities they are as follows: exaggerated sonority, rather frequent cracked pot sounds, exaggerated vibrations, amphoric breathing, sometimes gurgling sounds, which may change with the patient in different positions, pectoriloquy, a clear zone of sound in marked contrast to surrounding tissue, and sometimes a suggestion of Hippocrates succussion splash. Smaller cavities sometimes give intense and diffuse bronchophony.

Grancher believes that the diagnosis of a cavity is not difficult if it be large and contain little fluid, or if it be dry. He holds also that râles may mask the cavernous breathing and that caseous glands may compress a lobar bronchial and conceal the cavity. It has also been shown, as already noted by Aimard, that emphysema and pleural adhesions may interfere with the diagnosis of cavity.

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24 Paillard, H, and Robert, L. Quelques Points de Séméiologie des Cavernes Pulmonaires Tuberculeuses, *Progres méd* 27 462, 1911

Sternberg<sup>25</sup> states that coarse tubular sounds are pathognomonic with the same type of râles found with, or after, coughing. He considers the quantity of sputum important, while a continuous secretion of "suppurating" sputum indicates probable cavity. A quantity of sputum between 80 and 100 c c is significant. As is well known by percussion, a change in the quality of the note with the mouth open and when closed suggests cavity. Sternberg's modification of Wintz's phenomenon gives the following results with the mouth closed, light percussion elicits no abnormal sound. When the mouth is opened



Fig 7—Case 853. Roentgenogram of the lungs in a fairly early case with typical bronchial annular shadow extending from the first to the third rib on the right side. This shadow may be seen best by means of stereoscopy.

as widely as possible and uniform vigorous percussion is continued, a tympanic sound is elicited which decreases as the mouth is gradually closed. Sternberg also emphasizes the importance of the presence of large numbers of acid fast bacilli. The failure to obtain positive sputum is generally against cavitation.

<sup>25</sup> Sternberg, A. Zur Symptomatologie der Lungencavernen, St. Petersburg med. Wchnschr. 35 626, 1910.



King,<sup>26</sup> reporting on posttussive suction as a constant sign found in cavities, claims that whispering pectoriloquy in his experience is most fallacious. Posttussive suction has a high detached sound heard over certain cavities after coughing. It may vary in depth and intensity. He believes that it occurs most usually in old cavitations where there is a good deal of elastic fibrosis around the cavity. He agrees that firm pleural adhesions favor the production of the sound. It is not heard, however, in every case of cavity, but when heard it is a positive sign.



Fig 8—Case 960. Roentgenogram of the lungs in an advanced unilateral case. The original upper right lobe involvement is demarcated strongly and sharply by fibrous and pleural interlobar thickening. The large cavity has a heavy fibrous outline.

Norris<sup>6</sup> lays stress on the important and interesting question of the differential diagnosis between incipient tuberculosis, healed cavities and nontuberculous fibrosis. The fine, localized crackling râles which are heard at the end of inspiration and which often disappear on deep

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<sup>26</sup> King, D. B. The Value of Posttussive Suction as a Sign of Excavations in the Lung, *Internat Clin*, 15 S 4 61, 1906.

breathing cannot be confused with the longer, louder metallic clicks heard when a cavity is present. Likewise, the blowing amphoric note and whispered, cavernous pectoriloquy are not readily confused with the suppressed breath sounds, respiratory harshness or bronchial breathing found in incipient cases. Coughing, he says, will often cause signs of cavity to become more marked, gurgling râles originating in the cavity may also aid in the diagnosis. Norris believes that cavities are more frequently overlooked than erroneously diagnosed when absent. All wise statements are true if applied to a certain group of cases, but they cannot be expected to hold true for all cases.

Mantoux<sup>7</sup> believes that in tuberculous patients the clinical diagnosis should be made certain and confirmed by bacteriologic and roentgenologic examination. The three methods, he says, are equally indispensable, one corrects the error of the other. An examination of a tuberculous patient is incomplete if it does not rest on this diagnostic triad.

Fishberg<sup>8</sup> concludes by saying, "On the whole, cavities indicate chronicity of the tuberculous process in the lung." "It shows," he says, "that the resisting forces are active." From my experience in this institution I am of the opinion that such conclusions are erroneous (Tables 1, 2, 3 and 4).

Allyn<sup>2</sup> regards the following signs as most trustworthy in diagnosing a tuberculous cavity in the lung, deficient expansion or flattening of the chest wall over the cavity on breathing, high pitched tympany on percussion, especially if percussion is made with the mouth open, whispered pectoriloquy, cavernous breathing, multiplicity of râles, particularly moist râles which, after coughing, have a resonating quality. Rieder<sup>4</sup> points out the danger of infection of one part from cavities in another part of the lung.

Ribadeau-Dumas<sup>15</sup> concludes that clinical methods are insufficient. In eleven cases of tuberculosis with cavities the size of a large nut, but few were suspected during life.

Lhomme<sup>19</sup> believes that functional and physical signs of cavity are deceptive and that the diagnosis of cavities in infants is difficult.

Pallasse and Roubier<sup>12</sup> and Bernand and Tecon<sup>13</sup> point out that other diseases, such as dilatation of bronchi, pulmonary syphilis, post-pneumonic abscess, encysted pleurisy, partial pneumothorax, or gangrene, may be confused with tuberculous cavity signs.

I have already called attention in our cases to other conditions which have been diagnosed as cavities and others in which cavities were present, the physical signs being absent.

In order to establish the diagnosis of cavity by physical means, the presence of certain sounds and signs is necessary. The study of the skeletal and muscular asymmetry of the thorax is helpful—the demon-

TABLE 5—PHYSICAL SIGNS IN CAVITY AREA

Whispered Pectorillogy	Bronchovesicular Breathing	Bronchial Breathing	Feeble Breathing	Amphoric Breathing Sounds	Tinkling	Rales	Dullness	Diminished Resonance	Harsh Resonance	
+	++	+		2+		++	+	+		6 D
	+					++				7 H
+	+	+				++	+			46 G
+	+					++		+		71 A
+	+	+				++		+		70 F
+	+					++	+			96 B
+	+					++		+		123 S
+	+	+				++	+			127 M
+	+	+				++		+		125 S
+	+	+				++	+	+		128 G
+	+	+				++	+			150 G
+	+	+				++	+			170 F
+	+	+				++	+			178 S
+	+	+				++	+			204 T
+	+	+				++	+			225 U
+	+	+				++	+			227 O
+	+	+				++	+			228 C
+	+	+				++		+		237 G
+	+	+				++			+	238 Y
+	+	+				++	+			396 H
+	+	+			+	++	+		+	408 O
+	+		+			++	+			442 W
+	+					++	+			443 S
+	+					++		+		466 U
+	+	+				++		+		487 H
+	+					++		+		543 L
+	+		+	+		++		+		546 E
+	+		+	+	+	++	+	+		586 S
+	+		+	+		++	+	+		601 M
+	+	+				++	+	+		602 W
+	+					++		+		645 H
+	+					++		+		646 A
+	+			+	+	++	+	+		652 K
+	+					++	+	+		669 F
+	+					++	+	+		656 G
+	+					++	+			688 D
+	+					++	+			732 S
+	+					++	+			766 D
+	+	+				++	+			769 F
+	+					++	+			810 S
+	+					++			+	848 T
	+					++	+	+		930 D
	+					++	+			858 M
	+		+			++	+	+		936 L
						++	+	+		951 G

TABLE 6 — SUMMARY OF TABLE 5, SHOWING THE PHYSICAL SIGNS IN THE, CAVITY AREA IN FORTY-FIVE CASES

	Number of Cases	Percentage of Cases
Whispered pectorillogy	25	55
Bronchial vesicular breathing	35	77
Bronchial breathing	14	31
Feeble breath sounds	4	8
Amphoric breathing	3+ 71	8
Tinkling	3	6
Rales	42	93
Dullness	28	62
Diminished resonance	16	35
Harsh resonance	3	6

TABLE 7—POSTMORTEM FINDINGS AND ROENTGENOGRAPHIC FINDINGS COMPARED \*

No	Position	Postmortem Findings	Position	Roentgen Findings
7H	Left Right	A large cavity, upper lung, anteriorly, medially, and posteriorly Smaller cavities, middle of lung, medially	Left	1st rib, circular cavity, $5\frac{1}{2} \times 5\frac{1}{2}$ cm
71A	Right	A large cavity, upper lobe, anteriorly, laterally and medially	L & R	Apices, indefinite cavities of indefinite size
123S	Left Right	A large cavity, upper lung, anteriorly, medially and posteriorly Smaller cavities, middle lung, anteriorly, medially and posteriorly	Left	3d to 1st rib, irregular oval cavity, $5 \times 5$ cm
128G	Left	A large cavity, upper lung, anteriorly, medially and posteriorly	Left	1st to 3d rib, irregular oval cavity, $3\frac{1}{2} \times 3$ cm
150E	Right Left	A large multilocular cavity, upper lung, anteriorly and medially, a smaller cavity, lower lung, posteriorly An enormous cavity occupying the upper third of the lung	Left Right	1st rib up, irregular cavities, 3 cm + 3d rib up, multiple cavities
178S	R & L	Multiple cavities, upper lung, anteriorly	Left	Apex, circular cavity, $6 \times 6$ cm
225U	Right	A large cavity, upper lung, anteriorly, medially and posteriorly, 6 cm in diameter, 2 smaller cavities situated near the hilus of the lung, approximately 2 cm in diameter	L & R	Several cavities, 1st and 2d spaces, circular, $6 \times 2 \times 1\frac{1}{2}$ , right, $1 \times 1\frac{1}{2} \times 2$ , left
226C	Right	A large cavity, 8 cm in diameter, upper lung, anteriorly, posteriorly, and laterally, many smaller cavities below	Right	Multiple circular and oval cavities, 1st, 2d, 3d spaces, $2 \times 3$ cm +
227C	Left Right	A large cavity and many smaller ones, upper lung, anteriorly, posteriorly laterally Many large cavities, upper lobe, posteriorly, anteriorly, laterally and medially	Left Right	2d rib up, indefinite cavity, 5+ cm Over 1st rib, circular cavity, $3 \times 3$ cm
442W	Left Right	A multilocular cavity, upper lung, anteriorly, posteriorly and medially A cavity in the upper lobe anteriorly and lower anterior portion, several small cavities in mid portion, small cavity in mid portion of lower lobe	L & R	Multiple circular and irregular cavities, 3d rib up, 3 cm +
443E	Left	A large cavity and smaller cavities throughout upper half of lung, medially	Left	2d space, irregular circular cavity, $3 \times 3\frac{1}{2}$ cm
487H	Left Right	Lung collapsed Many small cavities throughout	Left Right	Cavity, pneumothorax 1st and 2d ribs, circular and oval cavities, $5 \times 4 \times 3 \times 4$ cm
546E	Left Right	Two large cavities, upper lung, medially Smaller cavities, upper lung, medially	L & R	1st and 2d space, oblong cavities $2 \times 1\frac{1}{2}$ cm
601M	Right Left	A large cavity, upper lung, anteriorly, medially and posteriorly, smaller cavities, middle and lower lung, anteriorly Smaller cavities, upper lung, anteriorly, medially and posteriorly	Right	Upper and middle, irregular oval cavities, 2 cm + and $6 \times 6$ cm
602W	R & L	Small cavities, upper lung, medially	R & L	Upper lobes, oval cavities, $6 \times 6$ and $6 \times 4$ cm
645H	R & L	Large cavities and multiple smaller ones, upper lung, anteriorly, medially and posteriorly	L & R	1st rib, oval and circular cavities, $6 \times 4$ , right, $6 \times 4$ , left
646A	Right Left	A large cavity, upper lung, anteriorly, medially and posteriorly Smaller cavities, upper lung, anteriorly, medially and posteriorly	Right	Middle and lower, indefinite and circular cavities, 2 cm + and $3 \times 2$ cm

TABLE 7—POSTMORTEM FINDINGS AND ROENTGENOGRAPHIC FINDINGS COMPARED \*—(Continued)

No	Position	Postmortem Findings	Position	Roentgen Findings
652k	Left Right	Many small cavities, upper lung A large cavity, apex, anteriorly, medially and posteriorly, 6 × 6 cm in diameter	Right Left	1st space, circular cavity, 5 × 4 cm Multiple, 3d rib up
688D	Left Right	A large cavity, upper and middle lung, anteriorly, medially and posteriorly A large cavity, middle lung, anteriorly, medially and posteriorly, small cavities, lower lung, medially	Left	Multiple, apex, 2d rib up, indefinite in size and shape
732S	Left Right	Large cavities, anteriorly medially and posteriorly, upper lung, multiple smaller cavities throughout outer portion, posteriorly Large cavities, upper lung, anteriorly, medially and posteriorly	L & R	Upper lobes, many oval and circular, right, 6 × 7, left, 3 × 1½ to 5 × 3 cm
766D	Left	A large cavity, upper lung, anteriorly, medially and posteriorly, smaller cavities, middle and lower lung, medially and posteriorly	Left	Multiple, 3d rib up, indefinite shape, 2+ cm in diameter
769F	Left Right	The whole lung, except a small area in the lower posterior is one large cavity A large cavity, 6 × 8 cm in diameter, apex, anteriorly, medially and posteriorly	Right Left	All lobes, circular and oval cavities 3 cm + 2d rib up
810S	Left Right	Large cavities upper lung, anteriorly, medially and posteriorly, multiple smaller cavities throughout middle lung, medially and posteriorly Large cavities, upper lung, anteriorly, medially and posteriorly	L & R	Multiple circular and oval cavities, 3d rib up, 3 cm +
930D	Left Right	A multilocular cavity upper third, numerous small cavities in midportion, anteriorly, medially and posteriorly Smaller cavities, upper lobe	Left Right	3d rib up, multiple indefinite cavities Over 2d rib, multiple indefinite cavities
951G	Right	A large cavity, upper lung anteriorly and posteriorly	Right	5th rib up, multiple circular cavities 4 cm +
1002T	Left	Numerous small cavities throughout	Right	4th rib up, multiple indefinite cavities
237D	Left	Numerous small cavities, upper lobe, varying in size from 1 to 8 cm, lower lobe, upper portion several cavities of not more than 15 mm	Left	Several small circular cavities, 1 cm and more

\* The postmortem findings as compared with the roentgenographic findings, in fourteen of the twenty-seven cases coming to necropsy showed that the position of the cavities was correctly diagnosed by roentgenograph, or 51 per cent, in ten cases, or 37 per cent, the position of some of the cavities was correctly diagnosed by roentgenogram, and in only three cases or 11 per cent, was the roentgenographic diagnosis shown by necropsy to be incorrect

stration of fixation or immobilization of a local area (say, for instance, the right upper portion from the third rib front) is important. An absence of movement in this area, or lagging in breathing, and an appearance of collapse in contrast to compensatory changes on the opposite side (that is, greater size, extension, more respiratory movement, greater filling and expansion), is of first consideration.

Consequently, by inspection and measurement much information can be obtained to aid in the more detailed diagnosis obtained by auscultation and percussion. The extent of the tuberculosis should be

determined first, the degree of apical involvement as compared with that at the base, whether there is hilus involvement, whether the pleura is affected, and to what extent, if any, the movements of the diaphragm are diminished

The duration of the disease, the chronicity of the process and the course of the infection are of assistance in diagnosing cavity. However, the lung should be in such a condition as regards the cavity that signs or combinations of sounds and conditions can be elicited and heard sufficiently clearly, intensely and constantly to be considered as diagnostic of cavity. The same rule holds good clinically regarding size, position, etc., of cavity as obtained roentgenologically.

In the patients examined at U S Army Hospital No 16 during the period of one year, 449 were definitely diagnosed as having tuberculosis of one or more lobes. We are, therefore, concerned with these cases, for among this number there occurred seventy-four cases of cavitation (Table 1). In the examination of the patients with cavitation the physical signs detailed in Tables 5 and 6 were found. Consequently, an analysis of the figures given here will aid in appreciating the subject as a whole.

# RAT BITE FEVER \*

## REPORT OF A CASE

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### DEFINITION

Rat bite fever (Sodoku of the Japanese, Rattenbisskrankheit, toxoinfection par morsure de rat, morbo da morso di topo, etc ) is an acute infectious disease caused by *Spinochaeta morsus muris*, following the bite of the rat (rarely cat, weasel, ferret or other animal) and characterized, after an incubation period, by recurring paroxysms of fever, a blue red exanthem, marked nervous symptoms, emaciation and weakness

### HISTORICAL

The disease is best known in Japan where it has long been endemic For a review of the history of this extremely interesting and rare disease the reader is referred to the excellent report of the disease in Japan by Miyake,<sup>1</sup> who, in 1900, found no cases recorded in the European literature In the older Japanese literature appear many references to a disease incident on the bite of the rat, but not fully described The first good description in modern Japanese publications appeared in 1890, in Katsura's system of surgery

Not only was the disease recognized early as being related to the bite of the rat in Japan, but it appeared also in the settlement days in our own country Several reports of an unusual febrile disease, accompanied by severe nervous symptoms, and following the bite of the rat are found in our early medical journals Of these, perhaps, the first is that of Dr Whitman Wilcox<sup>2</sup> published in 1840 Reporting an attack following the bite of a rat he states "Very little notice was taken of the wound until 12 or 13 days afterwards, when it commenced to be painful and tumefied I was called in on the evening of the 17th, and found him with pain in the back and head, heat of skin, thirst, tongue with a thin white coat, bowels costive, hand painful and swollen, pulse nearly natural, etc " He then describes severe mental symptoms, gangrene of the wound, with sloughing of the skin He also mentions a relapse occurring three or four days after subsidence of the first

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\* From the Department of Pathology and Bacteriology of West Virginia University School of Medicine

1 Miyake, H Ueber die Rattenbisskrankheit, Mitt a d Grenzgeb d Med u Chir 5 231, 1899

2 Wilcox, W Violent Symptoms from the Bite of a Rat, Am J M Sc 26 245, 1840

attack and lasting five to six days. This description corresponds closely with our present conception of rat bite fever. The characteristic exanthem and the lymphangitis and adenitis were not mentioned, however, nor was the relapsing type of fever carefully described.

In a study of the French literature, Roger<sup>3</sup> has found an excellent report of the disease made by Millot-Carpentier<sup>4</sup> in 1884, which leaves little doubt that his report of the disease was the first in Europe, and preceded the Japanese study of Miyake. In 1909, Horder<sup>5</sup> reported three cases from England. Crohn<sup>6</sup> in this country, reviewing the literature in 1915, found a total of fifty-two cases, and added one case which he reported. Blake,<sup>7</sup> in 1916, collecting the cases reported at that time, found a total of eighty-one on record in the entire literature.

I have found forty-eight cases reported since 1916 to July, 1919. These reports are given in the list of references. This makes the cases to date, including the eighty-one collected by Blake to 1916, number about 130.

#### INCIDENCE OF DISEASE

Cases have now been reported from Japan, France, England, the United States, India, Italy, Morocco, Scotland, China, Spain, Germany, Brazil, Australia and the Philippines. It is interesting to note that medical officers of the army have reported a number of cases among soldiers in the trenches in France and elsewhere. The similarity of the fever to trench fever, and the presence of obscure fevers, makes it necessary to keep this disease in mind in the trenches. A failure to obtain the history of a rat bite, or to recognize the cardinal symptoms of rat bite fever, might more easily occur among soldiers in active warfare.

The greater prevalence of the disease in Japan is probably due to the fact that more people live in wooden houses, where rats are numerous. Whether the percentage of infected rats is higher in Japan than in other countries cannot be known until a study of the prevalence of the spirochete in rats in different countries is made. According to Japanese investigators, the organism is found in from 3 to 12 per cent

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3 Roger, H. Erytheme toxi-infectieux et septicémie légère par morsure de rat des tranchées, un cas de sodoku fruste, *Marseille méd* **53** 321, 1916. Le cas français de sodoku, toxi-infection par morsure de rat, *Presse méd* **25**. 201, 1917. De l'ancienneté, en France, de la toxi-infection par morsure de rat (sodoku des Japonais), *Rev gen de clin et de therap*, *Par* **31** 323, 1917.

4 Millot-Carpentier. Considerations medico-physiologiques sur un cas de morsure de rat suivie d'intoxication ayant déterminé des accidents nerveux simulant l'hydrophobie et l'apparition d'un purpura à forme intermittente, *L'Union méd*, *Par* **38** 1069, 1884.

5 Horder, T. J. Rat Bite Fever, *Quart J Med* **3** 121, 1909.

6 Crohn, B. B. Rat Bite Fever, *Arch Int Med* **15** 1014, 1915, also, *Ref Handb M Sc*, New York **7** 483, 1917.

7 Blake, F. J. The Etiology of Rat Bite Fever, *J Exper Med* **23** 39, 1916.



of rats in that country. It is possible that the disease has been carried from Japan to other countries by infected rats. A study of infection in rats in different countries may help to determine this.

#### PREDISPOSING CAUSES

Age and sex seem to play no part in the occurrence of the disease. It has been found at various ages and in either sex. Occupation is important only in so far as it renders the person more liable to be bitten by rats. Hence more cases have been found among farmers, seamen, and soldiers in the trenches. Previous illnesses have no relationship to infection. Not all persons bitten by rats develop rat bite fever. There are a number of determining factors, such as (1) infection of the rat, (2) location of the wound—a wound on the exposed parts of the body is more likely to become infected than one through clothing, just as in rabies, (3) depth of the wound—in some cases a scratch has sufficed, in others free bleeding may cleanse the wound of infection, (4) mixed infection, which may inhibit growth of the spirochete or aid it. Cases have been reported of several persons bitten by the same rat, one developing the disease, another showing no symptoms (Miyake<sup>1</sup>).

#### THE CAUSE OF RAT BITE FEVER

Since the recognition of rat bite fever as a distinct disease, several reports of the discovery of a micro-organism associated with the malady have been published. The following may be mentioned: (1) *Streptothrix*, Schottmuller,<sup>8</sup> Blake, Tunnichliff,<sup>9</sup> Litterer,<sup>10</sup> Tileston,<sup>11</sup> (2) *Sporozoon*, Ogata,<sup>12</sup> (3) *Telosporidia*, Shikami, (4) *Diplococcus*, Middleton, Douglas, Colebrook and Fleming,<sup>13</sup> (5) *Spirochaeta morsus muris*, Futaki and associates,<sup>14</sup> Ishiwara and associates,<sup>15</sup> Ido and

8 Schottmuller, H. Zur Aetiologie und Klinik der Bisskrankheit, *Dermat Wchnschr* **58** 77, 1914.

9 Tunnichliff, R. *Streptothrix* in Bronchopneumonia of Rats Similar to That in Rat Bite Fever. Preliminary Report, *J A M A* **66** 1606 (March 25) 1916, *J Infect Dis* **19** 767, 1916. Tunnichliff, R., and Mayer, K. M. A Case of Rat Bite Fever, *J Infect Dis* **23** 555, 1918.

10 Litterer, W. New Species of *Streptothrix* Isolated from a Case of Rat Bite Fever, *J Tennessee M A* **10** 310, 1917.

11 Tileston, W. The Etiology and Treatment of Rat Bite Fever, *J A M A* **66** 995 (March 25) 1916.

12 Ogata, M. Die Aetiologie der Rattenbisskrankheit, *Deutsch med Wchnschr* **34** 1099, 1908, *Mitt a d med Fakult d k Univ z Tokyo* **8** 287, 1909, **9** 343, 1911, **11** 179, 1913.

13 Douglas, S. R., Colebrook, L., and Fleming, A. A Case of Rat Bite Fever, *Lancet* **1** 253, 1918.

14 Futaki, K., Takaki, I., Taniguchi, T., and Osumi, S. The Cause of Rat Bite Fever, *J Exper M* **23** 249, 1916. *Spirocheta morsus muris*, n sp., the Cause of Rat Bite Fever, *J Exper M* **25** 33, 1917.

15 Ishiwara, K., Ohtawara, T., and Tamura, K. Experimental Rat Bite Fever. First Report, *J Exper M* **25** 45, 1917.

associates,<sup>16</sup> Kitagawa and Mukoyama,<sup>17</sup> Kaneko and Okuda,<sup>18</sup> Kusama and associates,<sup>19</sup> etc

That the bite of an animal, especially the rat, may cause infection in man with different micro-organisms is obvious to anyone who makes a careful survey of the literature of diseases produced by animal bites (rat, cat, ferret, weasel, dog, mouse, etc) This is not at all surprising in view of the demonstration in rats of many parasites (streptothrix in bronchopneumonia of rats by Tunnichiff, *Spirochaeta icterohemorrhagiae* in rats by Ido in Japan, Noguchi,<sup>20</sup> Jobling and Eggstein in America, and a number of investigators in Europe, *Spirochaeta morsus muris*, Futaki and associates, Kusama and associates, Coles,<sup>21</sup> *Spuillum minor* Carter, *Spirochaeta laverani* Breml and Kinghorn, *Spirochaeta muris* Wenyon, which three may be similar to *Spirochaeta morsus muris* Futaki, spirochetes of Borrel, Calkins, Mezimescu, etc Still others may be present in the saliva of the rat, such as pathogenic streptococci, virus of rabies, etc) Mixed infections with more than one organism might, therefore, occur

From a study of the disease I am of the opinion that rat bite fever is caused by a specific micro-organism first observed by Futaki and his associates, *Spirochaeta morsus muris*, for the following reasons (1) The disease is a definite clinical entity, as will be described later (2) *Spirochaeta morsus muris* has been found in the blood and tissues of persons suffering from the disease, in the wild rat and field vole, all three strains belonging to the same species (3) The disease has been produced in animals by the bite of inoculated rats and pure cultures, and the spirochete found (4) Specific immune bodies, spirocheticidal and spirochetolytic) are present in the blood of patients (5) Arsphenamin has a specific therapeutic action in the disease

There are several difficulties in the way of demonstrating the specific organism in rat bite fever, and it is to aid in overcoming these

16 Ido, Y, Hoki, R, Ito H, and Wani, H The Rat as a Carrier of Spirochaetosis Icterohemorrhagiae, the Causative Agent of Weil's Disease (Spirochaetosis Icterohemorrhagica), J Exper M 26 341, 1917

17 Kitagawa, J, and Mukoyama, T The Etiologic Agent of Rat Bite Disease Preliminary Report Arch Int Med 20 317 (Sept) 1917 Kitagawa, J Clinical Experience with Cat Bite Disease, Saikingaku Zasshi, No 260, p 422, 1917, abstr in China M J 33 55, 1918

18 Kaneko, R, and Okuda, K A Contribution to the Etiology and Pathology of Rat Bite Fever J Exper M 26 363, 1917

19 Kusama, S, Kobayashi, R, and Kasai, K The Rat Bite Fever Spirochete, with Comparative Study of Human, Wild Rat and Field Vole Strains J Infect Dis 24 366, 1919

20 Noguchi, H Spirochaeta Icterohemorrhagiae in American Wild Rats, and Its Relation to the Japanese and European Strains, J Exper M 25 755, 1917

21 Coles, A C Rat Bite Fever, Lancet 1 350, 1918

that I wish to summarize our present knowledge of the disease. First, the rat that produces the bite is not obtained for examination. I have not been able to find a single report of such an examination. Not infrequently the rat is caught and killed, but there is a failure by the physician or patient, or both, to recognize its relation to the disease. Second, the spirochete is present in the blood, skin lesions and lymph glands in greatest number at the height of the first few febrile attacks, when smears and animal inoculations should be made. In some cases it may be absent from the blood, or there may be so few as to be overlooked. This will be discussed under diagnosis.

#### MODE OF INFECTION

The spirochete is inoculated in the tissues with the bite. It is present in the mouth of the rat probably from abrasions of the mucous membrane of the gums, as spirochetes have not been found in the mouths of experimentally inoculated rats, even when they have been able to produce the disease in other animals by a bite and when spirochetes have been present in the blood. Abrasions of the gums could easily occur. The germ has been found in the submucosa of the gums and also in the salivary glands of inoculated rats. It is present in the blood of these rats in considerable number about the eighth day after inoculation, also in the kidney and suprarenals.

Rats may also become infected by preying on infected rats and then transmit the disease by biting man or lower animals.

#### SPIROCHAETA MORSUS MURIS

This organism was first discovered by Futaki, Takaki, Taniguchi and Osumi in 1915. These investigators found a spirochete in the skin lesions, local lymph glands and blood of two of four cases. In the study of six other cases the following year they found the spirochete in five, in two of these it was found in the blood. Two types of spirochete were found, one, a short form, in the blood, the other a long form, in the tissues. Ishiwara and Ohtawara found a similar spirochete in animals infected by the bite of rats, confirming the findings of Ogata on infection by rat bite. In 1916, Futaki found that the two types are probably the same spirochete, intermediate forms also occurring. Kaneko and Okuda came to the same conclusion from the study of the pathologic anatomy of human cases in which they found the spirochete. Kitagawa and Mukoyama were able to infect rats, guinea-pigs and monkeys with an axillary lymph gland from a patient and found the same spirochete. Row<sup>22</sup> has observed a spirochete in rat

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<sup>22</sup> Row, R. On a New Species of Spirochete Isolated from a Case of Rat Bite Fever in Bombay, Indian J. M. Res. 5 386, 1917

bite fever in Bombay Sano,<sup>23</sup> and Costa and Troisier<sup>24</sup> have also found a spirochete in this disease. The organism has not yet been seen in cases in this country.

The spirochete varies in length from 2 to 6 microns, with its flagella it is from 6 to 10 microns long. The short form is usually found in the blood of patients and in experimental animals, and is probably the young form. The long form is found chiefly in human tissues, and in culture mediums. Intermediate forms and degenerating forms also appear. In cultures the organism is from 1.5 to 1.9 microns in length, thicker than the *Spirochaeta pallida*, and possesses one curve per micron. The curves are regular and sharp. There are usually from one and one-half to six curves, occasionally as many as nineteen. It stains readily with Giemsa's stain, also with Loeffler's methylene blue and gentian violet. It is gram-negative. Burri's india ink method is very satisfactory. Levaditi's method is best for staining the organism in tissues.

The organism is motile, having a rapid movement. Cultivated ones are less active. Infection occurs in the mouse, wild rat, guinea-pig and monkey. The guinea-pig and monkey develop the characteristic fever and other symptoms, whereas the other animals present the spirochete in great number in the peripheral blood without definite symptoms. In the mouse spirochetes appear in the blood from five to fourteen days after inoculation, and the animal usually survives. Mouse inoculation is a valuable aid in isolating the spirochete. In the guinea-pig the infection usually results fatally with swelling and congestion of the bitten part, enlargement of lymph nodes, fever, loss of weight and alopecia. Acute inflammatory changes are found in the kidney, and hyperemia and hemorrhages occur in the suprarenal where spirochetes are usually most numerous. Hyperemia of the lungs and catarrhal inflammation of the gastric mucosa also occur. In the monkey the symptoms are very similar to those in man and the infection is often fatal. However, a monkey recovered from the infection shows no symptoms on reinoculation.

In a very recent study by Kusama, Kobayashi and Kasai, which shows the human, wild rat and field vole strains of spirochete to be the same, the authors find that on inoculation of a rat or guinea-pig the spirochete for the first two weeks is found chiefly in the blood. Then it appears in the connective tissues of various parts of the body.

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<sup>23</sup> Sano, T. Rat Bite Disease. Case Report, Iji Shimbun, No. 981, p. 1153, 1917, abstr. China M. J. **32** 469, 1918.

<sup>24</sup> Costa, S., and Troisier, J. Un cas de sodoku (fièvre par morsure de rat), Bull. soc. med. de hôp. de Par. **40** 1931, 1916. Un nouveau cas de sodoku. Spirochetes a l'examen direct du sang, Bull. et mem. Soc. med. de hôp. de Par. **42** 616, 1918.

(submucosa of eyelids, lips, nose and tongue, capsule of lymph glands and salivary glands, adventitia of large blood vessels, parenchymatous organs) None are present in the normal saliva, intestinal contents or bile. They may appear in the urine.

That a streptothrix may be found in cases of rat bite fever was first demonstrated by Schottmuller, and later observed also by Blake, Tileston, Tunnichiff and Litterer. The fact that in some of these cases arsphenamin was used with prompt cure makes it very likely that the streptothrix was not the specific cause, but only a secondary invader. Recognizing the difficulties in finding the spirochete in blood smears, and also in obtaining positive animal inoculations when the blood and tissues are examined late in the disease or between paroxysms of fever, sometimes even during the attacks, one is not surprised at failure to find the spirochete in most cases of rat bite fever. Also the ulcerative endocarditis, and degenerative and infiltrative changes found in the organs in Blake's fatal cases are not demonstrable in experimental rat bite fever in animals, and have not been found in the other necropsies done on rat bite fever victims. I think that the specific action of arsphenamin, as found by Tileston, rules out the streptothrix as the cause of the disease in his cases.

#### SYMPTOMS

*A The Bite*—The bite is usually a small punctiform area which heals readily in a few days, the time depending on its size. It usually does not suppurate. In some cases, however, necrosis of the skin and subcutaneous tissue with sloughing, followed by slight pigmentation, occurs. Pus formation is due to secondary infection.

*B Incubation Period*—The average length of the incubation period is twelve days, it varies from five to thirty days. A few cases have been reported with symptoms manifested in less than five days, and some months after the bite. The latter cases were not controlled carefully, and probably were incorrect. In severe and prolonged cases, which seem to be more common after bites on the face or head, the incubation period is usually shorter than the average.

*C Prodromata*—As a rule, within two weeks after the bite the patient complains of pain and heat in the bitten area, which is swollen, of a bluish red color and somewhat indurated. The pain may become severe, being sharp or pulsating.

About the area of acute hyperemia may be a slight edema of the skin, giving a ring-like appearance about the central bluish red induration. Sometimes the bite resembles closely an extra-genital primary lesion of syphilis. Reddish streaks appear in the direction of the local lymph glands which soon become enlarged, tender, hard, but discrete.

The patient begins to complain of headache, pains in the muscles of the back and extremities and malaise. Soon the most constant symptom, the fever, appears.

*D Fever* —With the prodromal symptoms, inflammation of the bitten area, and lymphangitis and adenitis there usually occurs a sudden rise of temperature, from 102 to 105 F. It is ushered in with severe chills, great pains in the limbs, and headache. The pulse is rapid, full and soft. The patient often complains of great thirst, nausea and vomiting and a feeling of anxiety. The skin is pale, and the extremities are cold. In severe cases hallucinations, and even delirium or coma may accompany a fatal outcome during the first paroxysm of fever. The paroxysm usually lasts from three to six days, when it falls by crisis with profuse perspiration and great improvement in the condition of the patient.

After an apyrexia of from two to six days another attack occurs. In fatal cases the attacks may become more severe until death results. As a rule, subsequent attacks become less severe and less frequent until in a few months they disappear. The average duration of the disease is two months. However, Kitagawa and Mukoyama have seen a case with recurrences fifteen years after the first attacks, and Kusunoki states that one or two relapses per year occur for ten years after recovery from rat bite fever. The patients treated with arsphenamin seem to be entirely free from recurrences.

The fever not infrequently shows irregularity. At first it may be continuous or remittent. Later the attacks are of shorter duration and do not reach as high. On account of the variability of the fever, the cases may be classified into the following types:

- 1 Febrile form with exanthem
  - (a) Intermittent fever
  - (b) Continuous fever
- 2 Febrile form with nervous symptoms
  - (a) Acute
  - (b) Subacute
- 3 Afebrile form with marked nervous symptoms
- 4 Abortive form

The paroxysms may vary from one severe fatal attack, or one mild prolonged attack with continuous fever for as long as twenty days, to as many as thirty attacks. The average is about from five to ten attacks. They occur at least once a week at first. As already mentioned, they last from three to six days, to a day or less later in the course of the disease. The interval also varies somewhat, averaging four days.

*E Nervous Symptoms*—Involvement of the nervous system occurs in most cases of rat bite fever. There is usually severe headache, dizziness, ringing in the ears, blurring of vision, especially during the paroxysmal attacks of fever. In the acute cases delirium or coma may develop. Hemicrania, neuralgic pains and especially pains in the muscles of the extremities, mostly in the lower, occur. Beginning with the first or second attack of fever the pain may be generalized, and later remain localized in the lower extremities. In some cases persistent neuralgic pains have been recorded for months or years.

Motor disturbances may develop in the form of paresis of the lower extremities, rarely the upper, and they may become very marked. This usually disappears with recovery from the fever. The tendon reflexes may be exaggerated, less often abolished. Progressive atrophy of the extremities has been reported.

Sensory changes occur in most severe cases, from paresthesias to complete anesthesia in some areas, mostly the extremities. These usually last through the febrile period. Hyperesthetic or hypoesthetic zones may be found in different parts of the body.

The febrile type, with acute nervous symptoms, is suggestive of the symptoms of rabies. The patient complains of severe pain in the bite, dizziness, great anxiety, headache. Dyspnea, rapid and small pulse, sensory and motor disturbances of the extremities, collapse, delirium or coma and even death may follow.

There is also a subacute form. After the incubation period, with or without any exanthem, the patient complains of severe, persistent, muscular pains, there may be paralysis of the lower extremities, with loss of patellar reflexes. The motor and sensory disturbances may be of long duration.

In the abortive type the patient may have only a few mild attacks of fever, the exanthem may be confined to the region of the bite, or it may be entirely absent. There are vague general symptoms, malaise, headache, slight weakness. Recovery is rapid, usually in a week or two.

*F Skin Manifestations*—The exanthem is rarely absent, as in the mild or abortive cases. It usually makes its appearance with the first attack of fever and lasts several days, when it may disappear, leaving a slight pigmentation or desquamation. With the recurrence of the fever the exanthem usually reappears, or new eruptions become visible. Sometimes the rash is not visible until the second, third or later attack of fever.

It may affect the skin about the bite, or an extremity, or more frequently it appears on the face, neck, back, chest, abdomen and extremities and less often in the palms of the hands and on the soles of the feet. A rash on the mucosa of the mouth has also been

described. The rash is not symmetrical. It begins as a macular eruption, red to blue red in color, varying in size from 5 mm. to 10 cm., usually round or oval and well defined. Later the spots become elevated, the center may be higher than the periphery and paler in color. The color does not entirely disappear on pressure or only on deep pressure, which causes some pain. The areas are slightly indurated.

In cases where the rash is localized near the bite or on the extremity, large, bluish red, elevated, indurated areas appear, from a dime to the palm of the hand in size. They often are distributed along the course of the lymphatics and over the enlarged lymph glands. They are slightly painful on pressure.

Miyake has described an acute urticaria, which he states is very characteristic of the disease toward the end of its course. It is spread over the entire body, often accompanied by fever. It may be overlooked unless the patient is kept under observation until recovery is complete.

*G Lymphatics*—That the spirochete infection spreads at first by the lymphatics is indicated by the frequent occurrence of lymphangitis. Reddish streaks are seen extending from the bite to the lymph nodes of the area. These appear just before the first attack of fever and usually disappear entirely in a few days. Then the local lymph glands become enlarged, sometimes reaching the size of a hen's egg, though usually smaller than this. After the first three or four attacks of fever the glands return almost to normal, in some cases they remain large throughout the disease, enlarging and becoming painful with each attack of fever.

The glands do not suppurate. They are elastic, rather soft, and later become harder. There is pain on pressure, and often considerable tenderness. The enlargement is usually confined to the regional glands, though the others may also become affected.

*H Gastro-Intestinal Tract*—The gastro-intestinal symptoms are not severe. A white coated tongue, nausea and vomiting are not uncommon. Constipation is more often present than diarrhea. In a few cases severe dysphagia, almost resembling that of rabies, has been reported. The appetite is usually poor during the acute attacks, but may return to normal between the paroxysms.

The liver and spleen are not, as a rule, enlarged.

*I Genito-Urinary Tract*—Evidence of nephritis is found in about 10 per cent. of the cases. It may vary from an acute fatal parenchymatous nephritis to a mild attack. In the severe form there is a reduction in the urinary excretion, albumen, casts and some red cells are present in the urine. In other cases there is only a slight amount of albumen with few casts. That the spirochete has a tendency to attack



the kidney is also shown by its presence there in large number in experimental animals after inoculation

*J Circulation*—The pulse usually varies with the height of the fever. It is rapid and small. There may be evidence of myocardial weakness, probably due to the toxemia as well as the secondary anemia. In severe cases there may be palpitation of the heart, and a hemic murmur is often heard at the apex.

*K Respiratory Tract*—The respiratory system is little affected. Slight bronchitis may develop. In prolonged and fatal cases terminal pneumonia may occur. The dyspnea in severe cases develops with the high fever, and may be toxic in origin.

#### PATHOLOGY

Little is known of the pathologic anatomy of this interesting disease. Miura<sup>25</sup> examined one case seventeen hours postmortem, and found only an increase in the amount of cerebrospinal fluid and hyperemia of the pia mater. There were no specific changes in the internal organs. Histologic examinations were not made. Blake's case was a streptothrix septicemia, with localization of the streptothrix in the mitral valve, producing an acute endocarditis followed by infarct formation in kidney and spleen. Subacute lesions of the parenchymatous organs also were present. These degenerative and infiltrative changes have not been observed in experimental rat bite fever, nor in other postmortems in human cases, hence we are forced to conclude that they do not represent the picture of true uncomplicated rat bite fever.

In 1917 Kaneko and Okuda reported the findings in two cases. There were parenchymatous changes in the organs. In the kidney occurred hyperemia, swelling and degeneration of tubular epithelium. They report the presence of spirochetes in the kidney, in the cortex of the suprarenal and in the interstitial cells of testis. The liver presented fatty degeneration, necrosis chiefly in the centers of the lobules, hyperemia and hemorrhage. The local lymph nodes were hyperemic, with an inflammatory cellular hyperplasia, hemorrhages and erythrophagocytosis. Other lymph glands were swollen and hyperemic. Catarrhal changes in the mucosa of the stomach and urinary bladder, congestion of the lungs, and hyperemia and edema of the meninges occurred. Slight degeneration of muscle and nerve cells was found. At the site of the bite cellular infiltration, edema and degeneration (acute exudative inflammation) appear. There is frequently a lymphangitis extending from the bitten area to the lymph glands, shown by the presence of reddish streaks along the course of the lymph channels. This is followed by the lymphadenitis already mentioned.

In experimental guinea-pigs Ishiwara and others found swelling of the bitten area and lymph glands, acute inflammatory changes in the kidneys, hyperemia and hemorrhages of the suprarenals, hyperemia of the lungs and catarrh of the mucosa of the stomach Ido<sup>26</sup> has found similar changes in guinea-pigs infected by the bite of rats Futaki and his associates record swelling of the spleen, hyperemia, congestion and swelling of the liver, hemorrhages in kidneys and lungs of inoculated animals

The blood changes have been reported by several writers A leukocytosis occurs in most cases of rat bite fever, most marked during the attacks of fever It usually reaches from 13 000 to 20,000 cells and varies with the different attacks In most cases the count returns almost to normal between paroxysms The increase is often in the mononuclear cells, which may reach from 35 to 40 per cent of the white count However, others have reported a polymorphonuclear increase Eosinophils have been found by some to reach from 5 to 15 per cent In the case reported by me we found a leukocyte count of 16,000 one month after the bite of the rat and during an attack of fever The differential count showed 80 per cent of polymorphonuclears, 4 per cent of eosinophils, the rest were mononuclears During the afebrile condition the white blood count dropped to 9 600 and rose again to 15,000 at the next attack

There is usually a reduction in the red blood count with the development of the weakness and cachexia The red count in most cases examined has been about four million, and the hemoglobin, proportionately reduced, about 80 per cent Later an advanced anemia may develop

The Wassermann test is of interest because of the close relationship of *Spirocheta morsus muris* to the *Spirocheta pallida* Kitagawa and Mukoyama report a negative Wassermann in their case, and quote Kunusaki, who found the Wassermann negative in four of five cases of rat bite fever They also quote Inada as obtaining a negative Wassermann in Weil's disease, a spirochete infection On the other hand, Costa and Troisier, and Mauriac<sup>27</sup> obtained positive Wassermann in their cases The Wassermann was negative in the case reported by me It seems, therefore, that the Wassermann test is not to be depended on as an aid in the diagnosis of this disease In cases with a positive reaction, syphilis must, of course, be considered, as in the case reported by Brennemann<sup>28</sup> in a child with indications of congenital syphilis, whose mother gave a positive test

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26 Ido Y, Ito, H Wani H, and Okuda K Circulating Immunity Principles in Rat Bite Fever, J Exper M 26 377, 1917

27 Mauriac P Rat Bite Disease, J de med de Bordeaux 89.93, 1918

28 Brennemann, J A Case of Rat Bite Fever, Surg Clin 2 433, 1918

## DIAGNOSIS

The diagnosis of rat bite fever is based on

- 1 History of bite by rat or other animal
- 2 Cardinal symptoms, of which one or more are usually present
  - (a) Characteristic fever, usually relapsing
  - (b) Exanthem
  - (c) Muscular pains
  - (d) Nervous symptoms
  - (e) Lymphangitis and adenitis
- 3 Demonstration of *Spirochaeta morsus muris*
  - (a) In blood during febrile attack
  - (b) In area of bite, skin lesions or enlarged lymph glands
  - (c) Animal inoculation, preferably mouse in which spirochetes can be demonstrated in blood in from five to fourteen days, or guinea-pig, etc
- 4 Therapeutic test—administration of arsphenamin

In the differential diagnosis we must consider (1) erysipelas, (2) pyogenic infection (phlegmon or pyemia or septicemia), (3) relapsing fever, (4) trench fever, (5) malaria, (6) syphilis, (7) erythema multiforme

1 *Erysipelas*—This disease can be differentiated by finding the streptococcus, absence of characteristic exanthem of rat bite fever, temperature curve, course of the disease

2 *Pyogenic Infection*—In rat bite fever blood culture is negative, absence of suppuration in the bite, unless secondary infection occurs, characteristic fever, incubation period, eruption, history of bite

3 *Relapsing Fever*—Finding of spirochete of Obermeyer, number of attacks rarely more than three, short incubation period

4 *Trench Fever*—Spread by body louse, fever, relapsing or irregular, or continuous, sudden onset like influenza, nystagmus on extreme lateral rotation of eyeballs, enlarged spleen, harder than that in typhoid, macular rash, shin pains, painful joints without swelling, no laboratory diagnosis at present. Caused by resistant filterable virus

5 *Malaria*—Blood examination (*Plasmodium malariae*), therapeutic test by use of quinin, enlarged spleen, endemic character of disease

6 *Syphilis*—History of infection, examination of lesion for *Spirochaeta pallida*, Wassermann test, clinical manifestations

7 *Erythema*—Symmetrical arrangement of lesions, absence of history of external injury, recurrence of lesions, lesions of vivid color, often edematous, frequent association with rheumatism

## PROGNOSIS

The prognosis is usually favorable. The mortality has been about 10 per cent. The outcome depends on the severity of the disease. Cachexia, edema, nephritis, or severe anemia are bad signs. The patient is often incapacitated for a long time. The disease is more serious in very young or old people. A short incubation period followed by severe nervous manifestations usually indicates danger. Death may occur during the first few attacks of fever from severe toxemia. As already stated, attacks of fever may occur for years after the bite. The average course of the disease is from two to three months. With the use of arsphenamin the prognosis is very favorable, the symptoms usually disappearing after one or two injections. No recurrences follow this treatment, as a rule.

## TREATMENT

Prophylactic treatment consists of immediate cauterization of the bitten area with fuming nitric acid. The acid should be applied thoroughly in the bite, incision being done if necessary. Such treatment within an hour will usually prevent the disease and should be practiced in all animal bites. The ancient Japanese tried numerous odd cures, such as the use of poultices of herbs, filling the wound with gunpowder and then exploding it, applying raw meat and feeding it to a cat. Later reports have appeared in which quinin, iodid, salicylates and arsenic compounds by mouth were tried, but with no definite effect. In 1912, Hata<sup>29</sup> reported the use of arsphenamin in eight cases with complete recovery and disappearance of all symptoms in all but one case. Others have reported equally happy results. One or two injections usually suffice. The specific curative value of arsphenamin led Hata and others to suspect a spirochete as the cause of the disease. Mercury also seems to have a definite curative value (Borelli<sup>30</sup>). Arsphenamin has been found to have a curative value in experimentally inoculated animals. It should be given in all cases of rat bite fever.

## REPORT OF CASE

CASE.—An American boy, 9 years of age, was first seen by Dr. P. A. Gibbons, April 8, 1919. The history was as follows: March 25 the patient was bitten on the right index finger by a large gray rat while playing near his father's printing office. He reached his hand down into a barrel when the rat caught his finger, and according to the patient did not release its hold until it was killed by a person attracted by the screams of the boy. When the boy reached home the finger was painted with tincture of iodine. After

29 Hata, S. *Salvarsantherapie der Rattenbisskrankheit in Japan*, München med. Wchnschr. 59:854, 1912.

30 Borelli, E. *Mercurial Treatment of Rat Bite Disease*, Policlinico 25:25, 1918.

the bite he made no complaint and the wound seemed to heal nicely. On the fourteenth day he began to complain of pain in the finger and a burning sensation. The finger had become reddened and swollen. A physician was then called. He found the finger reddened, swollen, and at the site of the bite a slightly elevated blue red papule surrounded by a lighter edematous zone. The finger was painful on pressure. Examination revealed enlargement of the lymph glands in the right axilla. The supratrochlear glands were slightly enlarged. The physician made an incision but no pus was found. The area was swabbed with tincture of iodine. The boy returned to school the following day. Three days later (seventeen days after the bite) he complained of not feeling well, and the physician was again called and again incised the finger, finding very little pus. The symptoms were drowsiness, weakness, headache, diarrhea and vomiting. The gastric symptoms lasted for four days. April 11 the temperature was 102 F. The boy complained of chills and went to bed.

The patient was seen by me April 28. On this day his temperature was 99 F. He had suffered three attacks of fever, accompanied by severe headache, nausea and vomiting, pains in the back and extremities. These occurred at intervals of six days and lasted two to three days. During the third attack he became dizzy and fell. He was then sent to bed.

*Physical Examination*—April 28. Patient was pale, rather thin and had an anxious look. Temperature, 99 F., pulse, 90. The right index finger was bluish red, the color extending over the terminal phalanx. It was swollen and somewhat indurated. The incision had completely healed. On the right forearm were several bluish red, slightly elevated, well defined areas or nodules varying in size from a quarter to one inch in diameter. They were present on the flexor and extensor surface. Between them could be seen very faint reddish streaks. The supratrochlear glands were enlarged, measuring almost an inch in the greatest diameter. They were somewhat elastic and painful when compressed. The right axillary glands were also large, about the size of a walnut and not very hard. On questioning the patient and mother I learned that the skin nodules had first been seen about three weeks after the bite. A rash on the chest and abdomen was also reported to have been present. The rest of the body presented no eruption at this time. There was slight edema of the lower eyelids.

Heart and lungs. Negative.

Abdomen. Somewhat distended, suggesting slight ascites.

Liver. The lower edge was palpable along the free margin of the ribs, and flatness extended to the fifth interspace.

Spleen. Not enlarged.

Lymph glands. Right axillary glands enlarged, also supratrochlears. Other glands normal.

Head and neck. Negative.

Extremities. Negative, except for right arm already described.

Temperature. 99 F., pulse, 90, respiration, normal.

Urine. Amount, normal, acid, clear, specific gravity, 1.025. Albumin trace. Casts a number of hyaline and granular, no red blood cells.

Blood Examination. April 28, 1919. Erythrocytes, 4,100,000, leukocytes, 16,000. Differential count: polymorphonuclears, 80 per cent, mononuclears, 16 per cent, eosinophils, 4 per cent, hemoglobin (Sahli), 75 per cent.

Blood smears. Smears of blood obtained by puncture of the lobe of the ear were stained with Giemsa stain, Wright's stain, Jenner's stain and India ink. April 29 when the temperature had dropped to 99 F. All examinations were negative.

Blood cultures. April 29, 10 c.c. of blood were drawn from the arm, and 3 c.c. were placed in 200 c.c. each of plain bouillon and glucose bouillon, and

an equal amount in glucose agar (50 cc) for plating. The cultures were all negative aerobically. Unfortunately pressure of other work prevented animal inoculations at this time.

May 2 Temperature, 98.6 F. Erythrocytes, 4,600,000, leukocytes, 9,600, polymorphonuclears, 70 per cent, mononuclears, 27 per cent, eosinophils, 3 per cent. Blood smears stained with Giemsa and Jenner stain were negative.

Patient feels much better, but complains of weakness and loss of appetite. The skin nodules are much smaller and have almost disappeared. The right axillary glands are still enlarged. No rash is present on the body.

May 10 I was called to see the patient who had a severe chill and high fever on the evening of May 9. Temperature, 101 F, pulse, 100. The patient complained of nausea and severe headache. The nodules on the right arm were somewhat larger than on May 2, and pressure on the right axillary glands caused pain.

Blood examination. Erythrocytes, 4,400,000, leukocytes, 15,000, polymorphonuclears, 75 per cent, mononuclears, 23 per cent, eosinophils, 2 per cent.

Blood smears stained with Giemsa and Jenner failed to show any spirochetes after prolonged search. I inoculated two guinea-pigs with blood obtained from the left arm vein, using 3 cc intraperitoneally. The animals remained well for four weeks and showed no signs of illness whatever.

June 25 The patient felt much better but tired quickly. He complained of gastric disturbance. The nodules on the right arm had entirely disappeared. The right axillary glands were only slightly enlarged. The edema about the eyes had disappeared. The mother stated that the patient had lost about 20 pounds during his illness. From May 9 to June 25 the patient had two attacks of fever, but much less severe than the earlier attack and lasting only a day or two. I advised the administration of nearsphenamin intravenously. The patient had been treated symptomatically and was given Fowler's solution, from 3 to 6 drops, three times a day.

September 30 The patient felt well. The glandular enlargement had disappeared, and the patient had been free from attacks since July 28, when his temperature rose to 101 F.

Blood examination. Erythrocytes, 4,800,000, leukocytes, 9,000, polymorphonuclears, 76 per cent, mononuclears, 22 per cent, eosinophils, 2 per cent.

#### SUMMARY OF CASE

A boy, aged 9 years, was bitten on the right index finger by a rat, which instead of escaping, had to be killed in order to release its hold. The wound was shortly afterward painted with tincture of iodine and healed. After a period of fourteen days, inflammation, edema and induration occurred, accompanied by lymphangitis and lymphadenitis, and the appearance of a blue red exanthem. There were also high fever and chills, and gastric disturbances. This attack was followed by three others at intervals of about six days, each characterized by chills, fever, nausea, headache and pains in the extremities. Reappearance of the exanthem with these attacks was noted. There was marked lymphadenitis of the trochlear and axillary glands. The spleen was not enlarged. Slight nephritis existed. Blood examination revealed a leukocytosis, which reappeared with subsequent febrile attacks and returned almost to normal between paroxysms. Spirochetes or other organisms were not found in the peripheral blood, but the patient was not seen until thirty-four days after the bite. Inoculation of two guinea-pigs with blood obtained forty-six days after the bite proved negative. Cultures or animal inoculations were not obtained from the skin nodule or the local lymph glands. Blood smears made from the ear failed to reveal any spirochetes on several examinations, the first being made thirty-four days after the bite (twenty days after first paroxysm). The subsequent history reveals recurring attacks of fever at longer intervals, and less severe. No attack has occurred in the last two months.

The case is typical of rat bite fever, and of special interest because it calls attention to the presence of rats infected with the virus of the disease in this community. A study of rats for the presence of *Spinocheta moisis mureis* is now under way<sup>31</sup>

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# THE PROTEIN AND LIPIN CONTENT OF BLOOD SERUM IN THE NEPHRITIDES

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The changes that the blood undergoes in renal disease have of recent years received much attention, especially since the methods for examination of small quantities of blood for the nonprotein nitrogen fractions have been very ingeniously improved by various American scientists. The estimation of functional capacity of the kidneys as well as the art of prognosis and diagnosis have been much aided by these investigations. It is noteworthy, however, how comparatively slight is the attention that has been paid to the protein and lipin fractions of the blood of nephritic patients.

The first reliable estimation of the serum proteins was made in 1845 by Becquerel and Rodier, who reported that the total protein content was lessened in cases of Bright's disease, cardiac disease with edema and severe puerperal affections. C. Schmidt found the protein content much increased in cholera and diminished in nephritic individuals.

In normal subjects, the ratio of serum albumin to serum globulin is approximately from 1.5 to 2.0. It has been recorded by certain investigators that in chronic renal disease this ratio is markedly disturbed. In Table 1 an attempt has been made to gather from the literature the conflicting results reported. Mya and Viglezio summarized their findings as follows. In disease the albumin globulin ratio is much altered, the globulin increasing and the albumin diminishing. These alterations vary directly with those which occur in transudations. An increase of blood pressure increases the loss of albumin more than that of globulin. The investigations of von Limbeck and Pick and of Joachim seem to indicate that there is no disturbance in the albumin globulin ratio that should be especially characteristic of nephritis. Freund found that the globulin was reduced in nephritis.

In 1903, Erben reported that in chronic parenchymatous nephritis the globulin of the blood serum was much increased. But this did not seem to impress Morawitz, who, critically reviewing the literature on the subject in 1909, stated that no pathologic significance need be attached to the albumin globulin ratio changes in cases of nephritis. In this opinion, Ewing, von Noorden and others seem to concur.

TABLE 1—PROTEIN ESTIMATIONS OF BLOOD SERUM BY VARIOUS AUTHORS

Author	Condition	Albumin	Globulin
Hammarsten	Normal	4.52	3.1
Patein	Normal	4.63	2.77
v Limbeck and Pick	Normal	6.17-8.31	1.69-3.83
Rowe	Normal	5-6	1.6-1.7
Epstein		4.662	2.738
Estelle	Chronic Bright's disease	5.44	3.06
	Chronic Bright's disease	3.6	1.8
v Limbeck and Pick	Chronic nephritis	6.86	3.14
	Chronic nephritis	9.09	0.909
	Chronic nephritis	5.05	4.95
	Chronic nephritis	7.14	2.86
	Chronic nephritis	6.38	3.62
	Chronic nephritis	2.91	7.09
	Chronic nephritis	4.84	5.16
	Chronic nephritis	6.75	3.25
	Mediastinal tumor	6.41	3.59
	Hepatic cirrhosis	4.84	5.16
	Pneumonia	6.396	3.604
	Pneumonia	7.42	2.58
	Typhoid	6.15	3.85
	Febrile icterus	6.51	3.49
	Febrile icterus	8.28	1.72
	Pleurisy	2.60	7.40
	Erysipelas	6.21	3.79
	Meningitis	4.88	5.12
	Cancer of uterus	7.28	2.72
	Cancer of ovary	4.39	5.61
	Diabetes mellitus	5.56	4.44
	Diabetes mellitus	8.67	1.33
	Diabetes mellitus	8.32	1.68
	Diabetes mellitus	4.47	5.53
	Diabetes mellitus	4.61	5.39
	Diabetes mellitus	5.89	4.11
	Chlorosis	6.547	3.453
	Anemia	6.17	3.83
Erben	Subchronic nephritis	0.042	4.5317
	Chronic parenchymatous nephritis	0.2593	7.0352
	Contracted kidney	2.9942	2.5580
Oloetta	Eclampsia	3.42-5.21	1.86-2.31
Joachim	Chronic nephritis, uremia	6.238	3.761
	Chronic nephritis, uremia	5.327	4.672
	Cardiac disease	6.407	3.592
	Myocarditis	5.332	4.338
Freund	Pernicious anemia		33%
	Bright's disease		25 to 33%
Halliburton	Acute infectious fevers		Increased
Duceeschi	Thymectomy (dog)		
	Before convulsions	Increased	
	After convulsions		Increased
Epstein	Cardiac disease	4.417	2.240
	Chronic interstitial nephritis	4.310	2.396
	Chronic parenchymatous nephritis	0.466	3.462
Burekhardt, Wallerstein, Le winski, Githens	Starvation		Increased
Meyer, Hurwitz and Taussig	Antitoxic immunity		Increased
Rowe	Pneumonia	3.7	2.5
	Syphilis	5.0	2.5
	Chronic nephritis	3.9	2.4

In 1912 and 1913, Epstein published three papers recording the results of chemical studies on blood serums and puncture fluids. He concluded that the globulins were increased in cardiac disease associated with decompensation and serous effusions, in pulmonary and respiratory affections (inflammatory and noninflammatory), in diabetes mellitus and in chronic parenchymatous nephritis. So far as the last named disease is concerned, he definitely corroborated Erben's results, obtaining figures for the albumin globulin ratio which indicate the marked reduction of the albumin fraction and the enormous increase in globulin.

Based on his findings in nine cases of parenchymatous nephritis, in which, besides the globulin increase, he also found a huge amount of cholesterol in the serum, Epstein propounded his theory of the etiology of certain cases of chronic parenchymatous nephritis and of the causation of the edema in that disease. According to him, there is a group among the cases of chronic parenchymatous nephritis which is due to a constitutional disorder — of a metabolic or endocrine nature — in which the renal or other manifestations are concomitant or secondary in point of development and importance. He does not, however, describe cases of chronic parenchymatous nephritis in which the protein or lipin fractions vary from the “metabolic” (*sic*) type, and which he should point out as “nonmetabolic” in nature.

He ascribes the edema to the following factor: “The loss of protein incurred by the blood serum through the continuous albuminuria causes a decrease in the osmotic pressure of the blood, which fact favors the absorption or imbibition and retention of the fluid by the tissues.” The marked increase in the lipin content in these cases is taken as an evidence of the metabolic derangement of the organism, and to it is also ascribed some responsibility for the edema. On these findings, Epstein recommends for such patients a diet rich in proteins and poor in fats.

The theory of Epstein has points that are very appealing to the clinician who will venture anything to help his patient who has chronic edema. In practice, however, that group of which Epstein speaks, seems to be very rare. Of sixteen cases of chronic parenchymatous nephritis with marked edema and of seven with only slight edema, I have not found a single case which should have the marked protein and lipin deviations indicated by Epstein, or which should be benefited (in four of the cases in which the attempt was made) by a high protein fat poor diet.

In the examination of the patients, the blood was drawn before breakfast, and the blood serum was examined for the proteins by the method described by Morawitz. The cholesterol was determined by the method of Autenrieth and Funk as described by Hawk.

TABLE 2—SERUM ANALYSIS OF NORMAL HUMAN BEINGS

Case	Total Protein	Albumin	Globulin	Globulin, per Cent	Cholesterol, Mg per 100 C c
1	8.47	5.43	3.07	35	165
2	7.90	4.69	3.21	40	147
3	6.76	4.39	2.37	35	139
4	7.20	4.95	2.25	31	148

TABLE 3—SERUM ANALYSIS IN ACUTE AND CHRONIC INTERSTITIAL NEPHRITIS

Case	Total Protein	Albumin	Globulin	Globulin, per Cent	Cholesterol, Mg per 100 C c
Acute Nephritis					
1	5.80	3.62	2.24	38	157
2	7.15	4.37	2.78	38	162
3	6.79	4.14	2.65	39	139
4	7.06	4.25	3.71	46	185
5	7.76	3.96	3.80	48	167
6	7.65	4.73	2.92	38	160
Chronic Interstitial Nephritis					
7	8.67	4.89	3.78	43	220
8	7.42	4.37	3.05	41	180
9	7.06	4.44	2.62	37	175
10	6.53	3.88	2.65	40	164
11	7.07	4.32	2.75	38	210
12	8.66	5.73	2.93	34	193
13	7.53	4.86	2.67	35	139
14	7.74	4.59	3.15	40	148

TABLE 4—SERUM ANALYSES IN CASES OF CHRONIC PARENCHYMATOUS NEPHRITIS

Case	Total Protein	Albumin	Globulin	Globulin, per Cent	Cholesterol, Mg per 100 C c
1	6.00	3.72	2.28	38	155
2	7.42	4.75	2.67	36	174
3	6.78	4.41	2.37	35	183
4	4.24	2.93	1.31	31	194
5	5.90	3.72	2.18	37	167
6	5.81	3.37	2.44	42	139
7	5.58	3.41	2.17	39	225
8	7.00	4.26	3.34	44	184
9	5.76	3.75	2.01	35	137
10	5.73	3.84	1.89	33	173
11	6.09	4.14	1.95	32	275
12	6.16	3.76	2.40	39	216
13	6.74	3.93	2.76	41	274
14	6.75	4.05	2.70	40	139
15	7.13	4.14	2.89	42	164
16	6.82	4.37	2.45	36	144
17	6.41	4.17	2.24	35	153
18	7.33	4.62	2.71	37	149
19	5.72	3.95	1.77	31	162
20	7.73	4.72	3.01	39	166
21	6.04	3.87	2.17	36	156
22	6.03	3.08	2.95	34	165
23	6.47	4.27	2.20	34	172

TABLE 5—SERUM ANALYSES IN OTHER DISEASES

Case	Diagnosis	Total Protein	Albumin	Globulin	Globulin, per Cent	Cholesterol, Mg per 100 C c
1	Pleurisy with effusion	6.40	4.16	2.24	35	175
2	Pleurisy with effusion	7.48	4.19	3.29	44	220
3	Pleurisy with effusion	7.85	4.32	3.53	45	185
4	Pleurisy with effusion	6.95	4.17	2.78	40	147
5	Portal obstruction	7.07	4.10	2.97	42	239
6	Portal obstruction	6.69	4.22	2.47	37	226
7	Cardiac disease with edema	7.17	4.16	3.01	42	194
8	Cardiac disease with edema	6.69	3.95	2.74	41	148
9	Cardiac disease with edema	6.86	4.12	2.74	40	220
10	Diabetes	6.82	4.16	2.66	39	183
11	Diabetes	7.62	4.42	3.20	42	133
12	Diabetes	6.69	3.95	2.74	41	195

Without going into any painstaking argumentation, it will be seen that there is no protein change in the condition of chronic parenchymatous nephritis which is characteristic of that disease and which does not occur in the other types of the nephritides and in other diseases. The cases of so-called nephrosis which Epstein describes must be very rare, and it is possible that he has culled the instances which he reports from an extremely large number of cases of chronic parenchymatous nephritis in which the albumin globulin ratio in the serum is not markedly disturbed. If so, he fails to mention how rare these nephrosis cases are, and he fails to record his results with cases of chronic parenchymatous nephritis that are not in the so-called "metabolic or endocrine" group.<sup>1</sup> Several years ago,<sup>2</sup> I had the privilege of studying a patient who was suffering from nonparasitic chyluria, whose blood contained 320 mm of cholesterol. The urine contained very much albumin and fat. On feeding this patient on a diet poor in fat, we were able to reduce the fat in the urine very markedly, and also to diminish somewhat the protein excretion. Is it possible that this was a type of case that Epstein describes, in whom the constant excretion of huge amounts of lipins so irritated the kidney epithelium as to induce the marked albumin excretion?

On feeding patients suffering with chronic parenchymatous nephritis a diet of whites of eggs, skimmed milk, peas and lean meat for several days it was observed (Table 6) that the albumin globulin ratio was not affected, though there was some increase in the total protein of the blood serum. The edema, however, did not diminish in the slightest degree.

TABLE 6—EFFECT OF FEEDING A PROTEIN RICH DIET IN CASES OF CHRONIC PARENCHYMATOUS NEPHRITIS

Case	Period	Total Protein	Albumin	Globulin	Globulin, per Cent
4	Before	4.24	2.93	1.31	31
	After	5.27	3.59	1.68	32
8	Before	7.60	4.26	3.34	44
	After	7.75	4.50	3.25	42
9	Before	5.76	3.75	2.01	35
	After	6.12	3.92	2.20	36
11	Before	6.09	4.14	1.95	32
	After	6.37	4.46	1.91	30

It has been pointed out by Kerr, Hurwitz and Whipple that "there is a remarkable stability of the blood serum protein level in widely varying conditions of health and disease." Feeding of protein seems not to affect to any extent the serum protein content. Bohme and Reiss have shown, by the refractometer, that the concentration of

1 A personal inquiry directed to Dr. Epstein regarding these points remained unanswered.

2 Kahn and Sanes. Arch. Int. Med. 17: 181 (Feb.) 1916.

serum protein is only slightly changed after a large meal this change following no rule, being either an increase or a decrease (Rowe) The results of Rowe show that "after four days of high protein diet there is, on the average, a slight increase in the total proteins [with] no definite division of this increase between the albumin and the globulin fractions"

So far as the cholesterol content of the serum is concerned, one can only say that while, in general, there is an increase of this lipin in the blood serum in cases of chronic parenchymatous nephritis, this is by no means a universal rule It must also be observed that the cholesterol content is increased in certain other conditions, as, for example, in chronic interstitial nephritis, in diseases with serous effusions (at times), and in certain metabolic derangements

### CONCLUSIONS

1 In the series of cases investigated, I did not find one case of the so-called "metabolic or endocrine" type of chronic parenchymatous nephritis as reported by Epstein

2 The albumin globulin ratio does not seem to be markedly disturbed by various diseases

3 Feeding of patients suffering with chronic parenchymatous nephritis on a protein rich fat poor diet is a rather risky undertaking<sup>3</sup>

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## A STUDY OF THE COLLOIDAL GOLD REACTION AND ITS CLINICAL INTERPRETATION<sup>\*</sup>

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It was not until 1912 that Lange first presented the colloidal gold spinal fluid reaction which has since borne his name as well as the more common term, "gold-sol" reaction. In the comparatively short time which has elapsed since its advent, there has grown up on the subject a voluminous literature which has served to give the reaction a definite and well deserved place among the tests used as aids in the diagnosis of affections of the central nervous system. Further elucidation or discussion of the test may serve not so much for its justification as for a wider interpretation and broader understanding of this reaction and its relation to clinical symptoms. The best conditions for undertaking such a study will obtain, not in an insane hospital, dealing with mental cases alone, or even in a pure neurologic clinic, but in a general teaching hospital where all classes of cases are studied carefully from both laboratory and clinical points of view. In this manner an early diagnosis can often be made on patients admitted for other complaints, before the subjective symptoms are sufficiently developed to send them to nervous and mental specialists or to insane hospitals. In the medical department of the University Hospital routine spinal punctures are done, not only on the nervous and mental patients, but also in any cases showing signs of syphilis or in which a definite diagnosis cannot be made. Therefore, with this material at hand, there was undertaken a study of the colloidal gold reaction, consisting of the technic of the test, a résumé of previous literature and an interpretation of the "curves" based on these clinical and laboratory data.

First of all, in the study of any test, one must consider the allied reactions<sup>1</sup>. For globulin the Nonne test was most commonly used. This is done by mixing equal parts of supersaturated ammonium sulphate solution and spinal fluid. A white cloud or opalescence appearing in three minutes means an increase of globulin. In common with

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<sup>\*</sup> From the departments of pathology and neurology, University of Minnesota.

<sup>1</sup> The Wassermann tests were done in the department of bacteriology under the supervision of Dr. W. P. Larson. All the other reactions were performed by one of us.



Lee<sup>2</sup> and Hinton<sup>3</sup> we have had difficulty with this reaction, first due to hyposaturation, and later to an accidental substitution of magnesium for ammonium sulphate. Following the correction of these errors the test has been very satisfactory. More recently the Ross-Jones<sup>4</sup> ring test, a modification of the Nonne,<sup>5</sup> has also been employed. This consists of layering 1 c c of spinal fluid on 1 or 2 c c of a supersaturated solution of ammonium sulphate. A white or gray ring marking the point of contact of the two fluids constitutes a positive reaction. This has proved in our hands to be the most satisfactory globulin test. It is sharp, clear cut, easily read, and not often confused with a slightly opaque containing tube as is the Nonne. For some time the Pandy<sup>6</sup> reaction was employed in conjunction with the others, but was found to have no advantage over the Ross-Jones test, except that smaller amounts of spinal fluid might be used, and it has the disadvantage of being so sensitive that apparently positive results are frequently obtained, unconfirmed by other positive tests. Its technic consists of dropping one drop of spinal fluid into 1 or 2 c c of a saturated solution of phenol. The immediate appearance of a bluish white cloud signifies an increased globulin content.

For the cell count Alzheimer's method was not deemed feasible. Consisting as it does of celloidin embedding and sectioning of the centrifuged cells, it is of value only as a means of careful study and differential count of the individual cells, and is absolutely useless for a total count. From the point of view of both labor and time involved it is impractical for the routine laboratory worker. The method used in our laboratory is that described by Swift and Ellis<sup>8</sup> in which an ordinary counting chamber and pipet, such as is used for the counting of leukocytes, was employed. The diluting fluid consists of 10 per cent acetic acid with about 1 per cent of methyl violet to stain the leukocytes to distinguish them from the erythrocytes, and to make a differential count possible in the same preparation. This strength of acetic acid is sufficient to hemolyze the majority of the erythrocytes which may be present. The diluting fluid is drawn to the mark 1, then the spinal fluid is drawn to the mark 11, thus giving a very low dilu-

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2 Lee. A Simple Procedure for the Preparation of Colloidal Gold for Diagnostic Purposes, *Am J M Sc* **155** 404, 1918.

3 Lee and Hinton. A Critical Study of Lange's Colloidal Gold Reaction in Cerebrospinal Fluid, *Am J M Sc* **148** 33, 1914.

4 Ross. On the Use of Certain New Chemical Tests in the Diagnosis of General Paralysis and Tabes, *Brit M J* **1** 1111, 1909.

5 Nonne. Syphilis und Nervensystem, Ed 2, **105** Berlin, 1909.

6 Pandy. Ueber eine neue Eweissprobe für die Cerebrospinalflüssigkeit, *Neurol Centralbl* **29** 915, 1910.

7 Alzheimer. Einige Methoden zur Fixierung der zelligen Elemente der Cerebrospinalflüssigkeit, *Centralbl f Nerven u Psychiat* **6** 15, 1907.

8 Swift and Ellis. Cerebrospinal Fluid in Syphilis, *J Exp M* **18** 162, 1913.

As the cells of a normal fluid, at least, are few in number, it is best to count the whole nine square millimeters of the field, the number thus obtained being divided by nine to give the average per square millimeter multiplied by ten to get the number in 1 cmm. and finally by 250 for the dilution. In other words we use the following equation: the number of cells in the whole field being represented by X:

$$X \div 10 \div 9 \times 10 \div 9 = 100/81X, \text{ or roughly, } 1\frac{1}{5}X$$

The Fuchs-Rosenthal chamber has no advantage over the one mentioned above and is not as desirable for the ordinary laboratory as it cannot be used for other purposes. All cell counts done by us were made as soon as possible after the puncture was done, but the error on standing is not as great as is generally supposed. Our experience has been that if the fluid be well shaken each time the count will remain the same for from six to eight hours. Without the shaking, however, especially if the pipet be filled from the bottom of the tube the count rises slowly, pointing to the fact that the cells readily sink to the bottom rather than cling to the sides of their containing tube, as suggested by Swift and Ellis.

But it is in the preparation of the colloidal gold solution that every laboratory worker, whether amateur or experienced, comes to grief sooner or later. Most authors agree that a constant standard solution cannot always be made and that skill consists in ability to recognize and remedy the faulty solution. After months of success one is sometimes suddenly confronted by a so-called 'protected solution' or more rare, a hyperactive solution which gives the right curve but produces it with unusual rapidity and exaggerated color changes. However, there are almost as many suggestions for improvement of the method as there are writers on the subject. Glaser<sup>9</sup> being the exception in believing that it could never be made satisfactory. Lange<sup>11</sup> Eicke<sup>12</sup> Gruice and Moody<sup>13</sup> Jaeger and Goldstein<sup>14</sup> Kaplan and McClelland<sup>15</sup>

9 Fuchs and Rosenthal. Physikalisch-chemische zoologische und andere neue Untersuchungen der Cerebrospinalflüssigkeit. Wien. med. Presse 14: 2135-2242-2193, 1914

10 Glaser. Zur praktischen Brauchbarkeit der Lange'schen Goldsolreaktion in der Psychiatrie. Neurol. Centralbl. 33:688 1914

11 Lange. Die Ausfällung solch kleinen Goldes durch Cerebrospinalflüssigkeit bei gewissen Affektionen des Zentralnervensystems. Ztschr. f. Chemothrap 1:44 1912

12 Eicke. Die Goldreaktion im Liquor cerebrospinalis. München. med. Wertschr. 60:2715 1913

13 Gruice and Moody. Lange's Gold Chloride Test on the Cerebrospinal Fluid in Congenital Lues. J. A. M. A. 61:13 (July 2) 1913. Gruice and Moody. The Lange Gold Chloride Reaction on the Cerebrospinal Fluid of Infants and Young Children. Am. J. Dis. Child. 9:17 (Jan.) 1915

14 Jaeger and Goldstein. Goldsolreaktion im Liquor cerebrospinalis, Ztschr. f. d. ges. Neurol. u. Psychiat. 16:219 1913

15 Kaplan and McClelland. The Precipitation of Colloidal Gold. J. A. M. A. 62:511 (Feb. 14) 1914

Flesch,<sup>16</sup> Lee and Hinton,<sup>3</sup> Miller and Levy,<sup>17</sup> Eskuchen<sup>18</sup> Hammes<sup>19</sup> and Felton,<sup>20</sup> Harvey,<sup>21</sup> Kolmer,<sup>22</sup> Hulbert,<sup>23</sup> Speidel and Smith<sup>24</sup> all advocate their own methods or modifications which they find satisfactory. All authors agree, however, on certain essentials for a successful solution. These are (1) perfectly clean, hard Jena glassware, (2) water freshly double — or preferably triple — distilled in a glass still having no rubber connections, (3) chemically pure reagents, dissolved in the water mentioned above. The methods suggested for cleaning the glassware are many and include boiling with strong soap and water, washing with potassium bichromate or aqua regia, and followed by thorough rinsing in tap water. Our most satisfactory results have been obtained by rinsing all glass utensils with equal parts of concentrated hydrochloric and nitric acids, taking care that no small area on the inner surface escapes the process. They are then placed under running tap water until all the acid is removed. This is then followed by a rinsing with, first, ordinary distilled water, and then with distilled spring water. If this procedure is carried out on new glassware it need not be repeated as long as the utensils are reserved for this use only, as simply rinsing them in distilled spring water cleanses them sufficiently for use. During the past few months Jena glass has not been obtainable, but American made glass has served as well.

For the preparation of the reagent, 2,000 c c flasks, either the Erlenmeyer or round bottomed are found to be more satisfactory and more easily handled than beakers. In addition one needs one 10 c c pipet graduated in 1 c c and a 1 c c pipet graduated in  $\frac{1}{10}$  c c. In our experience the distilling of the water is the most important factor determining success or failure in making the solution. Any of the reagents if dissolved in improperly distilled water will spoil any solution for which they are used even if the bulk of the water be

16 Flesch. Die Untersuchung des Liquor cerebrospinalis mit kolloidalen Goldlösung, *Ztschr f d ges Neurol u Psychiat* **26** 318, 1914.

17 Miller and Levy. The Colloidal Gold Reaction in Cerebrospinal Fluid, *Bull Johns Hopkins Hosp* **25** 133, 1914.

18 Eskuchen. Die funfte Reaktion, *Ztschr f d ges Neurol u Psychiat* **25** 486, 1914.

19 Hammes. The Comparative Value of the Wassermann, the Colloidal Gold and Other Spinal Fluid Tests, *Am J M Sc* **154** 625, 1917.

20 Felton. Cerebrospinal Fluid and the Colloidal Gold Test, *New York M J* **105** 1170, 1917.

21 Harvey. The Colloidal Gold Test in Diagnosis, *California State J M* **16** 170, 1918.

22 Kolmer. *Infection, Immunity and Serum Therapy*, Ed 2, 1917, p 437.

23 Hulbert. Technical Improvement in Lange's Colloidal Gold Test, *J Mich M S* **15** 30, 1916.

24 Speidel and Smith. The Preparation of Colloidal Gold, *U S Nav M Bull* **12** 220, 1918.

satisfactory. Frequent distillations of our tap water failed to give water which would produce a proper solution, probably because of the chlorites added for the purpose of purification, which allowed volatile chlorine to come over into each freshly distilled solution. On the other hand, single distillation of spring water sold for drinking purposes gave perfect results. All of the difficulties of preparation (usually resulting in the so-called "protected" solution) in our laboratory have been traceable directly to the water. A similar idea as to the importance of properly distilled water is held by Black, Rosenberg and McBride,<sup>25</sup> but in addition they also place great stress on slow regular heating, while in our hands the mode of heating was found to be of little significance, the use of one small Bunsen flame giving just as satisfactory results as a powerful three-flame burner or the two used alternately on the same solution.

All solutions of our reagents were kept in stock, and were made from Merck products and distilled spring water. The only method ever employed here is that of Miller, Brush, Hammers and Felton.<sup>26</sup> One thousand c c of distilled spring water was heated slowly in a 2,000 c c flask to 50 C, then rapidly to 60 C, when 10 c c of a 1 per cent solution of gold chloride and 7 c c of a 2 per cent solution of potassium carbonate were added. At 80 C, 10 drops of a 1 per cent solution of oxalic acid were added. At 90 C the flask was removed from the flame and slowly, drop by drop, 5 c c of a 1 per cent solution of liquor formaldehyde was put in. The flask was then shaken until there appeared a pink color, slowly changing to a violet and then to a deep dark red, clear to both direct and transmitted light, and occasionally with a slight golden shimmer. In addition to having the proper color, this solution, when set up in the ordinary manner, must also remain unchanged when run with a known normal spinal fluid, give a typical curve with a known paretic fluid, 5 c c of it must be completely precipitated in one hour by 17 c c of 1 per cent solution of sodium chloride, and, most important of all, must be neutral to a 1 per cent solution of alizarin red in 50 per cent alcohol. The laboratory worker of today is deeply indebted to Miller and his associates for working out the method of determining the reaction of the solution and making it possible to correct each faulty one instead of frequently discarding large amounts.

The technic for testing the neutrality of the solution is very simple. To 5 c c of the solution in a test tube are added 2 or 3 drops of alizarin

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25 Black, Rosenberg and McBride. *The Colloidal Gold Test*, J. A. M. A. 69:1855 (Dec. 1) 1917.

26 Miller, Brush, Hammers and Felton. *A Further Study of the Diagnostic Value of the Colloidal Gold Reaction Together with a Method for the Preparation of the Reagent*. Bull. Johns Hopkins Hosp. 26:391 1915.

red as indicator From this it is determined whether an acid or an alkali is needed to bring it to the neutral point Ten clean test tubes are set up in a rack, and to each is added 1 c c of distilled spring water To the first tube is added 1 c c of fiftieth normal hydrochloric acid or sodium hydroxid, as the case may be, thus giving 0.5 c c hydrochloric acid or sodium hydroxid From this first tube 1 c c is transferred to the 1 c c of water in the second tube, giving 0.25 c c of the acid or alkali, and so on until the tenth tube contains only 0.0009765625 c c of the acid or alkali Then, to each tube are added two drops of alizarin red and 5 c c of colloidal gold The color changes from canary yellow in the acid, brownish red in the neutral, deep dark red in the faintly alkaline, to a deep purple in the strongly alkaline solution The tube showing the most typical brownish red is selected as the neutral, the amount of acid or alkali in that tube is divided by five to determine the amount necessary to neutralize 1 c c, this is multiplied by the number of cubic centimeters to be corrected and the resulting amount of the fiftieth normal hydrochloric acid or sodium hydroxid added to the solution, which is then ready for use The only point which may prove confusing to the amateur is the fact, not made clear in the literature, that a deep dark red with a purplish tinge in the upper layers when shaken, as well as the deep purple, is a definite sign of an alkaline solution, and that no red without a definite brownish tinge should be regarded as neutral

Craig<sup>27</sup> suggests placing 10 c c of colloidal gold solution and from three to four drops of the indicator in a glass beaker and titrating with the acid or alkali until the neutral point is reached But with such a confusing play of reds, browns and purples merging into each other it is practically impossible to recognize and stop at the neutral point, while in the method given above one may observe side by side the different color shades as brought about by the various dilutions and get a much more clear cut picture of the neutral point

After a satisfactory solution is once obtained, it appears to be very stable, and if kept corked in a dark cupboard will remain satisfactory for months The fine black precipitate or even the surface mold which occasionally appears in warm weather will not interfere with the reaction

A so-called "protected" solution, reacting neither to 1 per cent sodium chlorid nor to a known positive fluid, is usually alkaline Felton<sup>20</sup> considers that such a solution is due to an unusually wide distribution of the colloidal particles from slow or irregular heating We have found correct the observation of Craig that alkaline solutions are inert with a positive spinal fluid, slightly acid solutions will react

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27 Craig The Wassermann Test, 1918, p 213

as usual with paretic fluids, but with normal fluids will also give a curve similar to that of syphilis, while a strongly acid solution will give very little reaction with a positive fluid, but will show an abnormal reaction with normal fluids. Therefore, we agree with the majority of authors that a neutral solution is of the most vital importance. Moody<sup>28</sup> with ordinary precautions always obtains a neutral solution. Lee,<sup>2</sup> in contradistinction to practically all other observers, prepares his solutions with ordinary distilled water with no regard to age or method, uses only ordinary laboratory cleansing methods for his glassware, adds all reagents, except liquor formaldehydi, at once, pays no attention to neutrality, yet claims perfect results with all his solutions. But in our hands, as with most workers, a much more refined and careful technic seems necessary for satisfactory solutions and reactions.

The technic of setting up the test is very simple. Eleven clean test tubes are set up in a rack and to each is added 1 c c of a 0.4 per cent sodium chlorid solution. In the first tube is placed in addition 0.8 c c of the salt and 0.2 c c of spinal fluid, making 2 c c of a 1:10 dilution. From this tube 1 c c is removed and added to the 1 c c of salt in the second tube, making a dilution of 1:20. This is continued to the tenth tube which has a dilution of 1:5,120 and the last 1 c c of this dilution is discarded. Then add to each tube 5 c c of the colloidal gold solution and shake the tube well to facilitate mixture. The eleventh tube, therefore, contains only sodium chlorid and colloidal gold and serves as a control. The 4 per cent sodium chlorid may be kept as a stock solution instead of diluting a 10 per cent solution each time, as given in Lange's early technic. We have also found that this solution will prove just as satisfactory made up with ordinary distilled water as with double or triple distilled water.

A positive reaction, if present at all, begins to appear at once and then intensifies for several hours, being complete in from eight to twelve hours. As Solomon and Welles<sup>29</sup> have mentioned, all syphilitic curves appear the same at first with a "paretic" one developing later, and are only complete after twelve hours, so that if read too early a paretic curve may be confused with a syphilitic one. On the other hand, a test showing no beginning color changes at the end of one-half hour may as well be discarded, as none will appear later. For our readings we designate an unchanged fluid as 0, a bluish red as 1, a reddish blue as 2, a deep blue as 3, a gray blue as 4, and colorless as 5.

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28 Moody. Discussion, New York M. J. **105** 1170, 1917.

29 Solomon and Welles. Varieties of Gold Sol Test in Several Loci of the Cerebrospinal Fluid System, Boston M. & S. **172** 625, 1915, The Development of the Gold Sol Paretic Reaction as Compared with the Cerebrospinal Meningitis Type Considered from the Time Necessary to Form a Complete Reaction, *ibid* **174** 50, 1916, On the Value of the Gold Sol Test in Cerebrospinal Fluid Obtained Postmortem, *ibid* **172** 398, 1915.

Because of the peculiar shades all readings must be done with direct daylight, holding the tubes up against the sky instead of against green grass or colored buildings

The so-called typical "paretic" curve shows the first few tubes completely precipitated, giving a colorless solution, while lesser changes may appear in the remaining ones, e g, 5555543000 The syphilitic curve shows the first one or two tubes unchanged with the maximum color change (which is usually 3, seldom beyond 4) in the fourth or fifth tube, as 0023311000 This includes the curves of both tabes and cerebrospinal syphilis, as this reaction does not differentiate between them The so-called "meningitic" curve which does not distinguish between different types of meningitis or myelitis is designated by the early writers as "verschiebung nach oben," and consists of a curve showing color change in the right half of the tubes with the maximum reaction in the seventh or eighth, as 0000013310 Because of the possible nonsyphilitic causes, such as multiple sclerosis, of these zonal reactions, Felton and Maxy<sup>30</sup> make the timely suggestion of designating these zones by roman numerals rather than by terms such as "paretic" or "syphilitic" curves Thus, they call tubes with a maximum reaction and complete precipitation of from 1 10 to 1 160, zone I, those showing a reaction up to 4 and including dilutions of from 1 40 to 1 160 as zone II, and those showing the maximum color change beyond 1 160 as zone III

It is of interest to note the attitude toward this reaction of the authors who employed it during the trial period Lange concluded that the test was of importance in early diagnosis leading to early treatment, thereby preventing or modifying severe syphilitic and "metasyphilitic" diseases of the central nervous system Jaeger and Goldstein obtained characteristic curves in 100 per cent of cases of cerebrospinal syphilis and paresis Swift and Ellis, among the earlier workers in this country, used it in a few cases and concluded that it was no more delicate than the Noguchi butyric acid test Glasor felt that it was of no practical value because of the difficulty in preparing a satisfactory reagent Kafka<sup>31</sup> found difficulty in differentiating between cerebrospinal syphilis and paresis, but still considered it the most important of all spinal fluid tests Sippy and Moody<sup>32</sup> found it

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30 Felton and Maxy The Colloidal Gold Reaction in the Cerebrospinal Fluid in Acute Poliomyelitis, J A M A 68 752 (March 10) 1917

31 Kafka Ueber die Bedeutung der Goldsolreaktion der Spinalflüssigkeit zur Erkennung der Lues des Zentralnervensystems, Dermat Wehnschr 58 52, 1914 Kafka Ueber den heutigen Stand der Liquor diagnostic, Munchen med Wehnschr 62 105, 1915

32 Sippy and Moody The Colloidal Gold Reaction in the Diagnosis of Syphilitic and Other Lesions of the Central Nervous System, Trans Assn Am Physicians 28 720 1913

more sensitive and more exact than the Wassermann test and of especial value in differentiating between the various syphilitic diseases Eicke noted a parallelism between the colloidal gold curve and lymphocytosis Eskuchen found it to be of decided value not only in conjunction with other tests, but also independently Solomon and Koefod<sup>33</sup> considered it of great value as a diagnostic aid, but thought a "syphilitic curve" did not indicate syphilis unless supported by a positive Wassermann test Weston, Darling and Newcomb<sup>34</sup> considered the reaction a valuable addition to the Wassermann test, but found a few nonsyphilitic cases giving a "syphilitic curve" Lee and Hinton decided that the test did not parallel the others, but was usually corroborated by one other test, and also was more sensitive than the Wassermann Kaplan and McClelland obtained typical curves for all paretics and most tabetics, but not in all cases of cerebrospinal syphilis Flesch thought it more delicate and clear cut than the other tests Miller and Levy recognized the great value of the reaction, but pointed out that it did not differentiate between purulent and tuberculous meningitis, was inconstant in secondary and tertiary lues, and was useless in congenital syphilis Barnes and Ives<sup>35</sup> consider it of value when used with other tests even though they find that there is no characteristic curve differentiating tabes from cerebrospinal syphilis, that negative curves do not exclude syphilis and that, while it parallels other tests rather closely, yet it is not more delicate Solomon, Koefod and Welles<sup>36</sup> decided that the reaction was of the greatest value and should complete every spinal fluid examination, but that a positive reaction did not indicate syphilis unless supported by other tests Swalm and Mann<sup>37</sup> found no curves in their study of nonsyphilitic psychoses, yet did not always find the test specific for syphilis Miller and his associates felt that this reaction, while not replacing the other tests, has a sensitiveness and specificity not shared by the others, that the sources of error are few and easily recognized, and that the results are clear cut and decisive Solomon and Southard<sup>38</sup> found it to be

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33 Solomon and Koefod Experience with Lange's Colloidal Gold Test in 135 Spinal Fluids, Boston M & S **171** 886, 1914, Significance of Changes in Cellular Content of Cerebrospinal Fluid in Neurosyphilis, *ibid* **173** 996, 1915

34 Weston, Darling and Newcomb The Colloidal Gold and Other Tests Applied to the Spinal Fluid in Psychiatry, Am J Insan **71** 773, 1914

35 Barnes and Ives The Cerebrospinal Fluid in Syphilis of the Central Nervous System with Special Reference to Lange's Colloidal Gold Reaction, Interstate M J **22** 792, 1915

36 Solomon, Koefod and Welles The Diagnostic Value of Lange's Gold Sol Test, Boston M & S J **173** 957, 1915

37 Swalm and Mann The Colloidal Gold Test on Spinal Fluid in Paresis and Other Mental Diseases, New York M J **101** 719, 1915

38 Solomon and Southard Notes on Gold Sol Diagnostic Work in Neurosyphilis, J Nerv & Ment Dis **45** 230, 1917



of as much value on postmortem as antemortem fluids Hammes<sup>39</sup> thought that the colloidal gold test was more delicate than any other test and usually did not react with a negative fluid yet should be used in conjunction with the other tests Black, Rosenberg and McBride did not find this reaction appearing after provocative treatment, yet considered it to be the first of the reactions to appear in the development of the disease Lowrey<sup>39</sup> found it of immense value with, however, atypical positive curves in 10 per cent and decided atypical curves in 10 per cent more, yet no positive reactions with nonsyphilitic cases Harvey noted this test occasionally occurring alone in cerebrospinal syphilis and tabes He considered it of great value, nevertheless, he thought it should not replace the other tests Vogel<sup>40</sup> considered it of special value in tabes, but found a few syphilitic curves occurring in neurasthenia, "serous" meningitis, hemiplegias and chronic alcoholism Weston<sup>41</sup> raises the question of a positive reaction always indicating syphilis and reports three cases with paretic curves not accompanied by a history of syphilis, positive Wassermann, or luetin test Craig thought it the most valuable of all confirmatory evidence Rawlings,<sup>42</sup> while recognizing the importance of the colloidal gold reaction in general, considered it of especial value in differentiating between syphilitic and senile arteriosclerotic cases In her experience the cases in which necropsies showed syphilitic vascular lesions had shown syphilitic curves, while those of simple senile degeneration had shown negative reactions

#### CLINICAL INTERPRETATION

In the following analysis of over 800 spinal fluids from 408 patients we have grouped the cases, for purpose of study, under the following divisions (1) dementia paralytica, (2) tabes dorsalis, (3) cerebrospinal syphilis, (4) multiple sclerosis, (5) cord and brain tumors, (6) meningitis, (7) miscellaneous

Spinal punctures are done practically as a part of the routine examination on patients on the nervous and mental service and, also, in all medical cases presenting any evidence of involvement of the nervous system The diagnoses and laboratory findings were tabulated from the patients' clinical records

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39 Lowrey Cerebrospinal Fluid Tests, Especially the Gold Reaction, in *Psychiatric Diagnosis*, J Nerv & Ment Dis **46** 186, 1917

40 Vogel The Nature and Interpretation of the Colloidal Gold Reaction, *Arch Int Med* **22** 496 (Oct) 1918

41 Weston Does a Colloidal Curve Indicate Syphilis? *Am J Insan* **74** 431, 1918, The Colloidal Gold Precipitating Substance in the Cerebrospinal Fluid in Paresis, *J M Research* **34** 107, 1916, The Colloidal Gold Reaction, *Am J Syph* **3** 266 1919

42 Rawlings Colloidal Gold Reaction in 498 Psychiatric Cases, *Arch Neurol & Psychiat* **2** 180, 1919

The final diagnosis is made by the clinician at the time the patient leaves the hospital. He has the complete clinical and laboratory record before him, and, if a diagnosis of a syphilitic lesion of the nervous system is made when the laboratory tests are partially or completely negative, it is because the attending physician believes the clinical evidence justifies such a conclusion in spite of the lack of corroboration by biologic reactions.

In the summary of the tables under each heading in our discussion the figures represent the number of cases and percentages. Cell counts of five and less are called "negative," and cells counts of more than five are "positive." The sign " $\pm$ " refers to reactions that are "slightly" or "famly" positive, and if unaccompanied by other positive findings are ordinarily regarded as of no significance, this is especially true of the Nonne test.

#### DEMENTIA PARALYTICA

The value of the colloidal gold reaction in paresis is well recognized. It is rarely negative in untreated cases and commonly gives a curve in zone I. A reduction, at least in zone II, tends to persist even when the patient is receiving intensive treatment.

TABLE 1—RESULTS OF EXAMINATION OF CEREBROSPINAL FLUID BY MEANS OF NONNE, COLLOIDAL GOLD AND WASSERMAN TESTS IN DEMENTIA PARALYTICA

	Nonne	Cells	Colloidal Gold	Cerebrospinal Fluid Was- sermann
Total cases	19	19	18	18
+	14 = 73.68%	13 = 68.42%	17 = 94.4%	15 = 83.3%
$\pm$	2 = 10.52%			
=	3 = 15.78%	6 = 31.57%	1 = 5.5%	3 = 16.6%

In fifteen of the eighteen cases marked reactions were noted in zone I, in other words, a "paretic" curve. The one patient whose fluid was negative, except for a positive Wassermann, had received much treatment. Many authors have mentioned occasional nonsyphilitic cases, other than multiple sclerosis, which gave typical paretic curves. One such in our series (Case 16249), a case of brain abscess verified by operation, gave on two separate punctures a curve in zone I unsupported by other positive laboratory findings.

#### TABES DORSALIS

Of the spinal fluid reactions in tabes dorsalis, the colloidal gold is definitely the most valuable. In nine instances it was positive when the other tests were negative, and in seven other cases it was present with only one other positive reaction. If cell counts of nine and below

had been accepted as normal there would be only twenty cases, or 29.8 per cent, in which the cell count was "positive." Well marked curves were found in fairly early cases. In several patients given provocative treatment after one or more examinations had shown the fluid to be entirely negative we found the colloidal gold reaction to be the first to appear. In patients with a questionable clinical diagnosis of syphilis of the nervous system and whose spinal fluid is entirely negative, it is well worth while to give antisyphilitic treatment for three or four weeks and then to repeat the laboratory examinations at least twice with a week's interval between.

TABLE 2—GENERAL PARESIS

Hospital No	Nonne	Cells	Colloidal Gold	Wassermann
9478	+	29	5523211000	+
8497	++	26		
8589	+	20	5555444322	+
12625	+	20	5555430000	+
14031	++	50	5555322211	+
14163	++	5	4555322000	+
14338	++	40	5555433200	+
14401	++	5	255533100	+
14140	—	2	—	+
				— (history, much treatment) — early?
16189	+	5	0123311000	
H			1122333100	
M	+	281	4444311000	+
10602	++	60	5555554100	+
P	+	10	3555555100	—
9215	+	11	5554220000	+
12391	+	35	5554422000	+
12296	—	1	4442200000	—
9802	+	37	4443332000	+
16305	—	4	5544422000	+
16841	++	75	555555530	+

TABLE 3—TABES DORSALIS

	Nonne	Cells	Colloidal Gold	Cerebrospinal Fluid Was sermann
Total cases	71	67	74	72
+	31 = 43.79%	29(6+) = 46.3%	55 = 74.3%	38 = 52.6%
++	14 = 19.7%		4 = 5.4%	
—	26 = 37%	38(—5) = 53.7%	14 = 18.9%	34 = 47.3%
		Aver = 16.3%		

The cases that were diagnosed as tabes dorsalis in spite of negative spinal fluid reactions presented, as a rule, well marked signs and symptoms of the disease. One case (Case 16916) illustrates this very well. The patient gave a history of gonorrhea and a probable chancre eighteen years before, he complained of a swollen knee, girdle sensation, sphincteric and gastric disturbances. Physical examination showed Argyll Robertson pupils, incoordination, loss of deep pain sense in the calves and tendo Achilles, impaired sensation over the nose and across the chest, marked hypertonia, lost knee jerk on one

TABLE 4—TABES DORSALIS

Hospital No	Nonne	Cells	Colloidal Gold	Wassermann
9183			11233210000	+
9436	±	31	—	— (Cerebrospinal syphilis)
9530	±	1	—	—
9726	+	48	5443320000	+
9087	+	22	1223321000	(50%)
9183		1	1123321000	+
8876	+	7	5544421000	+
7955	+	7	0124321100	+
7727	±	7	223333200	+
8404	—	1	—	—
11582	—	1	—	— (much treatment)
12611	±	1	2233320000	+
12753	—	1	—	—
12309	—	1	—	—
12511	+	80	4555555544	+
12056	±	6	1123100000	+
10752	—	0	—	+
10977	±	5	2233320000	+
11018	+	15	2223332000	+
10681	+	5	2223322000	+
12956	+	22	2223320000	+
12831	+	3	1113320000	+
13068	+	30	1133332000	+
12753	—	1	—	—
13342	+	125	1123210000	+
14441	—	?	1112311000	+
10933	±	3	012311000	—
10367	±	3	0012320000	—
14470	—	2	001233321	—
10552	+	5	0013321000	—
13000	+	15	2223100000	+
14257	+	250	2223442100	+
14442	—	1	—	—
10215	+	5	5555542200	—?
10797	+	?	0023332100	—
12627	±	24	1133320000	+
12966	+	3	4433321000	+
13016	+	36	112332100	+
14201	—	1	—	—
14474	—	2	—	—
14521	+	3	1122330000	+
14491	+	80	1112311000	+
14636	—	2	—	— Treated
14857	—	1	—	—
14512	—	2	0031100000	+
15857	—	21	2233320000	+
15695	±	8	1223331000	+
15808	+	10	1223210000	+
15695			2233332000	+
S	+	10	0001121000	+
B	—	1	00123321	—
A N	—	1	0002100000	—
N	±	3	0013332000	—
W	+	30	0013100000	—
16137	—	1	—	—
K	—	4	0012210000	—
B	+	20	0123332000	+
S	+	3	0012210000	—
F	—	20	1233210000	+
H	+	25	455554200	+
A J	—	1	2223310000	—
B	±	2	1122210000	—
C	—	6	000011233	—
16386	—	2	0013220000	—
MeQ	+	5	0113320000	—
16495	+	45	0123334100	+
16656	+	12	0013331000	+
15549	±	2	4433332100	+
14470	—	2	0012332100	—
16393	—	3	—	—
16843	±	1	0012311000	—
16840	++	45	0225555551	+
C	+	?	0013441000	(also pachymeningitis)

side, and a typical Charcot joint of the other knee Six spinal fluids all from different punctures were entirely negative The blood Wassermann, however, was always positive in this case

#### CEREBROSPINAL SYPHILIS

The value of the colloidal gold test is strikingly shown in the series of cases of cerebrospinal syphilis Eighty-five per cent of the fluids gave some reduction, and 75 per cent definite curves On the other hand, the Nonne was positive in 63 per cent, and definitely positive in only 31 per cent, there was a cell count above five in 45 per cent, and above nine in only 31 per cent The Wassermann was positive in 48 per cent In 18 per cent of the cases the colloidal gold was the only reaction that gave evidence of a pathologic condition of the cerebrospinal fluid The fluids from cases of cerebrospinal syphilis tend to give a reduction in zone I, somewhat more frequently than those from cases of tabes dorsalis It has been suggested by Solomon and Welles that the curve of cerebrospinal syphilis is a "forme fruste" of the curve commonly found in dementia paralytica

TABLE 5—CEREBROSPINAL SYPHILIS

	Nonne	Cells	Colloidal Gold	Cerebrospinal Fluid Was sermann
Total cases	27	27	27	27
+	11 = 40 74%	12 = 44 44%	21 = 77 79%	13 = 48 14%
++	6 = 22 22%		2 = 7 4%	
---	10 = 37 03%	*15 = 55 55%	4 = 14 8%	14 = 51 85%

\* If cell counts below ten are regarded as normal, then there were only nine positive cell counts or only 31 per cent

#### MULTIPLE SCLEROSIS

Miller, Brush, Hammer and Felton reported three cases of disseminated sclerosis, all giving "paretic" curves Hammes examined the fluid in four cases and only one gave the curve of paresis Flesch found a "paretic" curve in six out of eight cases Kaplan<sup>43</sup> saw such a curve only once in eighteen cases Oetiker<sup>44</sup> obtained a reduction of the colloidal gold in one case Kaplan and McClelland, Vogel, De Crinis and Frank<sup>45</sup> each reported two cases giving one paretic and one syphilitic curve Craig found the results in multiple sclerosis to be indefinite Solomon and Koefod reported four cases, two gave a "paretic" curve, one a "syphilitic" curve, and one was negative

43 Kaplan General Paresis, New York M J 100 397, 1914

44 Oetiker Erfahrungen mit der Langeschen gold sol Reaktion im Liquor cerebrospinalis, Ztschr f klin Med 82 235, 1915

45 De Crinis and Frank Ueber die Goldsol reaktion im Liquor cerebrospinalis, München med Wchnschr 61 1216, 1914

Solomon and Southard suggest that the positive colloidal gold reductions in these cases may be due to the substance produced in the process of atrophy and sclerosis. Of the conditions other than syphilis and meningitis giving a well marked curve, multiple sclerosis is the one most frequently met. While often emphasized that the curve in disseminated sclerosis resembles that of paresis, it is our experience that the curve is more frequently in zone II, as is illustrated by the fact that nine of our twenty-two cases gave curves of this type, while only two cases were in zone I. The finding of an average cell count of 14 in multiple sclerosis as against the average of 16 in normal fluids is interesting in that it tends to confirm the theory of a toxic etiology in this disease.

TABLE 6—CEREBROSPINAL SYPHILIS

Hospital No	Nonne	Cells	Colloidal Gold	Wassermann
14203	+	300	5555443311	+
14408	—	10	0002232100	+
13946	+	18	—	—
14143	—	1	—	—
14177	—	1	—	— (20 ars-phenamin treatments, much Hg)
12878	+	12	2223322000	+
8512	+	1	1112333210	+
7796	—	1	0122210000	—
8081	—	70	2555443321	+
8607	+	170	2222211100	+
12114	+	1	0343332200	+
14140	—	1	—	—
10393	+	12	0112333000	—
80867	+	3	0012320000	—
12680	+	1	1112220000	—
9218	—	1	0013321000	—
14444	+	50	4222200000	+
14408	—	9	0002232100	+
14833	—	1	0002332100	—
15858	—	1	0001232000	—
15990	—	6	0012221000	+
16159	+	235	2444333211	+
15847	+	2	4433332100	+
16530	+	1	0012200000	+
16847	+	1	0123331000	—
16890	+	9	0144442000	—

TABLE 7—MULTIPLE SCLEROSIS

	Nonne	Cells	Colloidal Gold	Cerebrospinal Fluid Wassermann
Total cases	21	20	20	21
+	2 = 9.52%	7 = 35%	9 = 45%	
±	4 = 19.04%		2 = 10%	
—	15 = 71.42%	13 = 65%	9 = 35%	21 = 100%

## BRAIN AND SPINAL CORD TUMORS

Although generally overlooked in the literature, we feel that a curve in zone III, especially unaccompanied by meningitic symptoms, is of very definite diagnostic value as indicating meningeal irritation, as shown in cases of tumors of the brain or spinal cord. In our series of fourteen cases of such a condition, each verified by operation or

TABLE 8—MULTIPLE SCLEROSIS

Hospital No	Nonne	Cells	Colloidal Gold	Wassermann
8977	—	6	1111000000	—
12010	—	1	—	—
12237	—	1	—	—
10222	++	2	—	—
12950	—	1	—	—
13005	—	1	—	—
14086	—	25	1133220000	—
13691	—	8	0323100000	—
13189	++	7	0122110000	—
14517	++	3	2331000000	—
14814	—	1	—	—
9948	++	4	5433310000	—
10117	++	10	2333200000	—
10466	—	2	—	—
14821	—	2	—	—
16079	—	8	1122331100	—
16422	—	2	0012100000	—
16464	—	2	—	—
16775	+	0	1555552200	—

TABLE 9—MENINGITIS

Hospital No	Nonne	Cells	Colloidal Gold	Wassermann	Type
9117	+	32	1100000000	+	Tuberculosis
8599	++	112	0000000123	—	Tuberculosis
B	+++	300	0114444321	—	Pneumococcus
O	+++	340	0000002321	—	Tuberculosis
16780	++	281	0003555410	—	Tuberculosis
H	++	220	0000124442	—	Tuberculosis

TABLE 10—TUMORS OF BRAIN AND CORD

	Nonne	Cells	Colloidal Gold	Cerebrospinal Fluid Wassermann
Total cases	14	10	14	14
—	6 = 42 55%	3 = 30%	8 = 57 1%	1 = 7 64%
++	2 = 14 28%	—	1 = 7 1%	—
—	6 = 42 55%	7 = 70%	5 = 35 7%	13 = 92 85%

TABLE 11—CORD AND BRAIN TUMORS

Hospital No	Nonne	Cells	Colloidal Gold	Wassermann	Type
9333	—	1	—	—	Gliosarcoma
9066	+	30	0002333210	—	Gumma
8809	—	13	0002333100	—	Gumma
8170	+	2	0011223334	—	Sarcoma of spine
11487	++	5	2222333311	—	Glioma
12783	—	—	—	—	Sarcoma of cord
13715	—	4	—	—	Gumma
10393	++	12	0112333000	+	Gumma
9720	++	5	0000012222	—	Sarcoma
13570	—	—	—	—	Cerebellar sarcoma
16399	—	0	—	—	Brain tumor
16249	—	1	4444320000	—	Brain abscess
16669	++	4	0000012555	—	Cord tumor
M	++	4	0000012555	—	Cord tumor

necropsy, such a curve was present in eight cases. This is of special value when found in these conditions accompanied by negative or faintly positive Nonne and a low cell count, while meningitis, on the other hand, has its curve accompanied by ++ or +++ Nonne and a high cell count.

#### MISCELLANEOUS CASES

Our series of miscellaneous cases is made up of general medical and surgical cases, neurologic cases not coming under any of the special headings, and cases of syphilis where the central nervous system is not definitely involved. Of this group, twenty-five fluids gave some curve including four very slight reductions—not over “1”, only fifteen were curves that are ordinarily regarded as significant. Eight of these were in cases which presented clinical or laboratory evidence of syphilis, of which three had involvement of the nervous system (sciatica, myelitis and paralysis agitans).

TABLE 12—MISCELLANEOUS CASES

	Nonne	Cells	Colloidal Gold	Cerebrospinal Fluid Was sermann
Total cases	243	233	240	239
+	10 = 4.11%	15 inc = 230 cases	7	0
±	12 = 4.94%	6 and over = 3 cases	14	0
—	221 = 90.95%	Aver = 1.618		239

Of the seventeen nonsyphilitic cases giving curves

12 had involvement of the nervous system

3 = tumor of cord or brain

2 = progressive muscular atrophy

2 = nonsyphilitic myelitis or encephalitis

2 = multiple neuritis (very slight reduction)

1 = essential epilepsy (very slight reduction)

1 = sciatica

1 = Alcoholic psychosis

5 showed no neurologic findings

1 = acute bronchitis

1 = chronic vulvitis

1 = reserved diagnosis

1 = myxedema

1 = cirrhosis of the liver

Of the three cell counts over 6 one was a case of syphilis with a cell count of 12 and a slight colloidal gold curve, one was a case of psychasthenia and gave a count of 6, and the third was a case of “optic atrophy” with a slight positive Nonne and a cell count of 8.



TABLE 13—MISCELLANEOUS CASES

Hosp No	Diagnosis	Nonne	Cells	Colloidal Gold	Wassermann
7894	Cardiac syphilis	—	1	0001210000	—
8493	General syphilis	—	1	—	—
9633	Syphilis of bladder	—	2	—	—
10953	Tertiary syphilis	—	1	—	—
10893	Syphilis of tibia	—	5	—	—
10894	General syphilis	—	2	—	—
10323	General syphilis	+	1	—	—
10684	General syphilis	—	2	—	—
11253	General syphilis	—	1	—	—
11481	Tuberculosis of larynx and syphilis	—	12	1112210000	—
11981	Nephritis and syphilis	+	1	1112210000	—
12680	General syphilis	+	1	1112220000	—
12601	General syphilis	—	1	1133321000	—
					(Dispensary case)
12996	Syphilitic iritis	—	2	—	—
14324	General syphilis	—	1	—	—
14229	General syphilis	—	1	—	—
14329	General syphilis	—	1	—	—
15959	General syphilis	—	1	—	—
15943	Syphilitic aortitis	—	3	—	—
16103	Paralysis agitans and syphilis	—	3	0012221000	—
16236	Congenital syphilis	—	1	—	—
16510	Aortic aneurism	+	2	00013411000	—
8699	Combined sclerosis	—	1	—	—
8150	Permeious anemia	—	2	—	—
9637	Permeious anemia	—	2	—	—
10222	Combined sclerosis	+	2	—	—
10712	Combined sclerosis	—	1	—	—
13569	Permeious anemia	—	1	—	—
13868	Combined sclerosis	—	1	—	—
14794	Combined sclerosis	—	3	—	—
15696	Permeious anemia	—	1	—	—
15803	Permeious anemia	—	1	—	—
16709	Combined sclerosis	—	0	—	—
9850	Seiatic and syphilis	+	2	012322000	—
11316	Seiatic	—	1	—	—
12874	Seiatic	—	1	—	—
13162	Seiatic	—	1	—	—
14035	Seiatic	—	2	—	—
14318	Seiatic	+	4	1133310000	—
16345	Seiatic	—	1	—	—
9827	Epilepsy	—	1	—	—
10832	Epilepsy	—	2	—	—
11211	Epilepsy	—	1	—	—
12823	Epilepsy	—	1	—	—
12527	Epilepsy	—	1	0111000000	—
13582	Epilepsy	—	1	—	—
14832	Epilepsy	—	2	—	—
14040	Epilepsy	—	4	—	—
14435	Epilepsy	—	1	—	—
14435	Epilepsy	—	2	—	—
14591	Epilepsy	—	1	—	—
16262	Epilepsy	—	3	—	—
Λ	Epilepsy	—	1	—	—
9860	Paralysis agitans	—	3	—	—
11137	Paralysis agitans	—	1	—	—
14449	Paralysis agitans	—	3	—	—
16263	Paralysis agitans	—	1	—	—
5	Paralysis agitans	+	4	—	—
16796	Paralysis agitans	—	1	—	—
14449	Paralysis agitans	—	1	—	—
9766	Multiple neuritis	—	2	—	—
10763	Chronic lead poisoning	—	—	0012210000	—
10464	Polynuritis	—	2	1111000000	—
10657	Chronic neuritis	—	3	—	—
15431	Postdiphtheritic paralysis	—	1	—	—
9279	Hemiplegia	—	1	—	—
11217	Thrombosis of cerebellum	—	2	—	—
13377	Hemiplegia	—	1	—	—
13710	Old hemiplegia	—	1	—	—
13226	Hemiplegia	—	1	—	—
13461	Right hemiplegia	—	2	—	—
16076	Cerebral hemorrhage	+	2	—	—
16176	Cerebral hemorrhage	—	2	—	—
16725	Cerebral hemorrhage	—	3	—	—

TABLE 13—MISCELLANEOUS CASES—(Continued)

Hosp No	Diagnosis	Nonne	Cells	Colloidal Gold	Wassermann
9963	Muscular dystrophy	—	1	—	—
10128	Bulbar palsy	—	1	—	—
10272	Progressive muscular atrophy	—	1	11132100000	—
12041	Progressive muscular atrophy	+	—	1111100000	—
14641	Amiotrophic lateral sclerosis	—	2	—	—
14586	Progressive muscular atrophy	—	2	—	—
15964	Progressive muscular atrophy	—	3	—	—
14641	Amiotrophic lateral sclerosis	—	3	—	—
9751	Transverse myelitis	—	1	—	—
10740	Myelitis	+	1	0000022245	—
14715	Encephalitis	—	1	—	—
16204	Myelitis, syphilitic	—	5	2223310000	—
16369	Myelitis	+++	1	0124444444	—
11319	Traumatic neurosis	—	1	—	—
11622	Neurasthenia	—	1	—	—
11410	Traumatic neurosis	—	1	—	—
12270	Neurasthenia	—	1	—	—
13088	Neurasthenia	—	1	—	—
13062	Neurasthenia	—	2	—	—
13650	Neurasthenia	—	1	—	—
13628	Hysteria	—	1	—	—
13679	Neurasthenia	—	1	—	—
13118	Neurasthenia	—	1	—	—
13143	Neurasthenia	—	1	—	—
13481	Hysteria	—	3	—	—
13807	Hysteria	—	1	—	—
14020	Neurasthenia	—	1	—	—
14487	Neurasthenia	—	1	—	—
14588	Hysteria	—	1	—	—
14384	Neurasthenia	—	1	—	—
14186	Neurasthenia	—	—	—	—
14285	Neurasthenia	—	1	—	—
14558	Hysteria	—	2	—	—
14402	Neurasthenia	—	0	—	—
14680	Psychasthenia	—	1	—	—
15939	Neurasthenia	—	1	—	—
15921	Neurasthenia	—	2	—	—
16094	Neurasthenia	—	1	—	—
16149	Neurasthenia	—	1	—	—
16428	Hysteria	—	1	—	—
14384	Psychasthenia	—	6	—	—
10665	Dementia praecox	—	1	—	—
14565	Dementia praecox	—	1	—	—
14442	Senility	—	2	—	—
14532	Dementia	—	1	—	—
16111	Senility	—	1	—	—
K	Melancholia	+	1	—	—
16759	Cyclothymia	—	1	—	—
G	Alcoholic psychosis	—	0	0013110000	—
8743	Senile paraplegia	—	4	—	—
9336	Optic neuritis	—	1	—	—
10965	Chronic progressive chorea	—	1	—	—
10591	Pachymeningitis	—	1	—	—
11299	Syringomyelia	—	1	—	—
12935	Fracture of skull	—	1	—	—
13000	Myasthenia gravis	—	1	—	—
13661	Hydrocephalus	—	1	—	—
13729	Cervical rib	—	1	—	—
13775	Cervical rib	—	1	—	—
13959	Fracture of spine	—	1	—	—
14591	Cerebellar atrophy	—	2	—	—
14590	Lateral sclerosis	—	2	—	—
15826	Caries of vertebrae	—	2	—	—
D	Optic atrophy	±	8	—	—
16440	Chorea	—	1	—	—
12408	Myxodema	—	3	0121000000	—
14231	Hyperthyroidism	—	1	—	—
15812	Adenoma of thyroid	—	2	—	—
15922	Exophthalmic goiter	—	2	—	—
16758	Hyperthyroidism	—	2	—	—
10631	Obesity	—	2	—	—
16694	Obesity	—	0	—	—
11214	Diabetes mellitus	—	1	—	—
14475	Diabetes mellitus	—	3	—	—
16194	Diabetes mellitus	—	1	—	—
14475	Diabetes mellitus	—	1	—	—

TABLE 13—MISCELLANEOUS CASES—(Continued)

Hosp No	Diagnosis	Nonne	Cells	Colloidal Gold	Wassermann
8845	Chronic valvular disease	—	1	—	—
9949	Mitral stenosis	—	2	—	—
10550	Aneurism of aorta	—	—	—	—
12238	Angina pectoris	—	1	—	—
13476	Arteriosclerosis	—	3	—	—
13802	Arteriosclerosis	—	5	—	—
13937	Chronic endocarditis	—	1	—	—
13555	Chronic myocarditis	—	1	—	—
14206	Valvular disease	—	1	—	—
14234	Cardiac	—	1	—	—
15934	Mitral stenosis	—	2	—	—
16205	Arteriosclerosis	—	1	—	—
15840	Lymphatic leukemia	—	1	—	—
16337	Acute pericarditis	—	0	—	—
16699	Cardiac disease	—	2	—	—
16216	Arterial calculus	—	0	—	—
10760	Arteriosclerosis	—	1	—	—
10912	Bronchitis	—	1	—	—
10494	Pulmonary tuberculosis	—	2	—	—
10551	Acute bronchitis	—	1	0022100000	—
10639	Pulmonary tuberculosis	—	1	—	—
14332	Pulmonary tuberculosis	—	1	—	—
15033	Miliary tuberculosis	—	3	—	—
15970	Asthma	—	4	—	—
15704	Pulmonary tuberculosis	—	1	—	—
16464	Chronic pulmonary lesion	—	2	—	—
16346	Pneumonia	—	4	—	—
16880	Acute miliary tuberculosis	—	1	—	—
10379	Arthritis	—	1	—	—
11727	Multiple arthritis	—	1	—	—
14251	Chronic arthritis	—	3	—	—
15944	Arthritis	—	2	—	—
16784	Chronic polyarthritis	—	1	—	—
10956	Gastric carcinoma	—	1	—	—
12497	Carcinoma of prostate	—	1	—	—
16808	Diffuse carcinomatosis	—	2	—	—
9957	Gastric carcinoma	—	1	—	—
9653	Refractive error	—	1	—	—
10337	Refractive error	—	1	—	—
12733	Reserved	—	2	—	—
12450	Reserved	—	1	0011100000	—
12489	Reserved	—	1	—	—
10980	Gingivitis	—	1	—	—
16535	Gingivitis	—	2	—	—
12054	Duodenal ulcer	—	2	—	—
16552	Duodenal ulcer	±	2	—	—
16073	Duodenal ulcer	—	1	—	—
13551	Cystitis	—	1	—	—
14406	Chronic cystitis	—	1	—	—
14406	Chronic cystitis	—	3	—	—
14483	Appendicitis	—	1	—	—
14483	Appendicitis	—	2	—	—
14114	Chronic amygdalitis	—	2	—	—
16763	Amygdalitis	—	1	—	—
14487	General debility	—	2	—	—
S	General debility	±	3	—	—
9859	Hereditary contraction of finger	—	2	—	—
10898	Atrophy of testicle	—	3	—	—
10720	Pregnancy	—	—	—	—
10180	Chronic gastritis	—	1	—	—
11077	Adhesions of cecum	—	1	—	—
11173	Prolapsed urethra	—	1	—	—
12213	Psychitis	—	1	—	—
12639	Chronic vulvitis	—	1	0012210000	—
10796	Ulcer of foot	—	1	—	—
12128	Inguinal hernia	—	1	—	—
12968	Chronic nephritis	—	1	—	—
13392	Fracture	—	1	—	—
13324	Periostitis of os calcis	—	1	—	—
14021	Pyelonephrosis	—	1	—	—
14413	Visceroptosis	—	2	—	—
14781	Infectious diarrhea	—	1	—	—
16237	Nephrolithiasis	—	4	—	—
16604	Cholecystitis	—	1	—	—
16433	Gastric ulcer	—	4	—	—

It is not at all improbable that the six syphilitic cases, coming, as they did, to our attention because of the positive blood Wassermann only, and giving no definite clinical evidence of involvement of the nervous system, will eventually develop clear cut signs of neurosyphilis. Of the thirteen definitely positive curves, twelve occurred in cases either of general syphilis or disease of the nervous system.

This series shows quite conclusively that even a very slight precipitation of the colloidal gold is suggestive of involvement of the nervous system and a reduction of any magnitude is a definite indication of such a condition, and also that a negative curve, especially when unaccompanied by clinical symptoms is definite ground for ruling out organic lesions of the central nervous system. Although our series of cases of epilepsy is too small to justify any conclusions concerning the colloidal reaction in this disease, it is of interest to note that not one curve was found. While, on the other hand Larkin and Cornwall<sup>46</sup> in 114 colloidal gold tests done on epileptic patients obtained no curve in 46 per cent, a low curve to "2" in 46 per cent, and a higher curve to "3" in 8 per cent.

#### VALUE OF COLLOIDAL GOLD TEST IN TREATED CASES

In reviewing the literature one is impressed with the great variance of opinion on the value of the colloidal gold test in treated cases. Lange in his first presentation of the test claimed that it closely paralleled the clinical course. Eskuchen noted a general paresis curve change to a syphilitic curve. Solomon and Koefod found no marked change of the curve in treated cases, and concluded that there was no relation between the curve and the duration and severity of the disease. Swalm and Mann stated that in remissions and treatment a paretic curve may be lost or changed to one of a syphilitic type. Black, Rosenberg and McBride thought that the colloidal gold test was the last reaction to become negative under treatment, and also saw it change in type during the process. Mehrtens<sup>47</sup> found the reaction steadily decreasing and becoming atypical under treatment. De Crinis and Frank found that as a patient improves the colloidal gold curve returns to normal. Farnell<sup>48</sup> noted that paretic curves under prolonged mercurial or arsenical treatment decreased in intensity, but a few remained unchanged even under prolonged intraspinal treatment. Hammes found that a change in the curve during treatment rarely

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<sup>46</sup> Larkin and Cornwall. Spinal Fluid in Epilepsy, *J Lab & Clin M* 4:352, 1919. Larkin. Laboratory Diagnosis in Neurosyphilis, *Am J Syphilis* 3:76, 1919.

<sup>47</sup> Mehrtens. Discussion, California State M J 16:170, 1918.

<sup>48</sup> Farnell. Observations on the Colloidal Gold Reaction, *Providence M J* 16:158, 1915.

occurred Miller and Levy considered that the reaction remained unchanged, both in remissions and under intensive intraspinal treatment, in their series only one case showed a curve diminishing with clinical improvement Ayer<sup>49</sup> observed that all spinal fluid tests are of little value in indicating progress under treatment Grulee and Moody reported one case of congenital syphilis which gave a positive colloidal gold reaction at six weeks of age, which, under treatment, became negative at thirteen weeks, and therefore they concluded that treatment modifies the reaction but to a less degree than the Wassermann Kaplan and McClelland found that the paretic curve resists all treatment and consider the condition analogous to that known as "Wassermann fast" Solomon and Southard noted that any one test may remain positive after all the other tests become negative, therefore, concluded that the laboratory reactions never parallel the clinical findings Cornwall<sup>50</sup> notes that a curve may be temporarily increased after treatment

Our series of treated cases is too small and the results are too variable to permit of any conclusions The following observations, however, may be of some interest

Our usual method of treatment in the hospital consists of weekly intravenous injections of arsphenamin (occasionally neoarsphenamin) followed by spinal drainage twenty minutes later, this treatment is preceded by a few doses of mercury and iodids, which treatment was sometimes continued during the intravenous treatment, the arsphenamin being alternated with the mercury A few of the earlier cases were given arsphenaminized serum intraspinaly It is noteworthy that with this method of therapy the fluid not infrequently gave more marked reactions after the second or third treatment, or became positive where negative on the first examination In later examinations the fluids tended to be less "positive" In a few of our cases all the spinal tests gradually returned to normal under intensive treatment, but even in these the reactions showed no uniformity in the order of their decrease or disappearance

Many of the fluids, however, gave little or no indication of change of reaction while, at the same time, the patient gave marked clinical evidence subjectively and objectively of betterment Therefore, one is justified in the assumption that the colloidal gold curve, while of very definite value in initial diagnosis, is often practically useless in treated cases, either for diagnosis or prognosis, and has been found not to

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49 Ayer Rational Use of Spinal Puncture, *J Nerv & Ment Dis* 46 429, 1917

50 Cornwall Syphilis in Its Relation to the Central Nervous System, *Mil Surgeon* 43 510, 1918

parallel clinical symptoms This is well illustrated by several of our cases in which at times during courses of treatment negative curves were obtained and in which later typical reactions resulted

In our experience, fluids showing pronounced curves did not change to any marked degree during treatment, while provocative or slight reactions often gave temporarily or permanently negative findings

We had opportunity of examining the fluids of several patients at intervals covering months or a year and more, and it was interesting to note the constancy of the colloidal gold curve One patient who was receiving intensive treatment gave practically the same curve for three years

#### GENERAL DISCUSSION

The foundation for the colloidal gold reaction was laid by Zsigmondy,<sup>51</sup> who found that "certain colloids, especially proteins," had a protective action on the precipitation of colloidal gold suspensions by sodium chlorid—an electrolyte The protective value of each protein examined varied, different amounts of each protein being necessary to protect 5 c c of colloidal gold against 0.5 c c of a 10 per cent solution of sodium chlorid It was Lange, however, who applied this test to the quantitative study of the protein in the cerebrospinal fluid Lange considered it as an indication of the mixture of the protein, but Weston has shown that the substance is dialyzable through thimbles impermeable to albumins and can be precipitated by ammonium sulphate and is, therefore, a globulin

Zaloziecki<sup>52</sup> thought it was an immunity reaction Jaeger and Goldstein regarded it as a physical phenomenon, probably of an electrical nature Eskuchen looked on the cause of the precipitation as due to the pathologic increase of the albumin, variations in the type of precipitation are apparently caused by various forms of physico-chemical relations of the albumin

Solomon and Koefod experimented on adding arsphenamin to the gold solutions, they obtained definite color reactions, but found that normal spinal fluids in varying dilutions up to 1:5,120 protected the solution against this color change Felton said the zonal reactions are caused by the interrelationship of the globulin and albumin, the albumin protects and the globulin precipitates the gold

In considering the comparative worth of the various tests used in the clinical study of cerebrospinal fluid it must be borne in mind that each test depends on a different substance in the cerebrospinal fluid

<sup>51</sup> Zsigmondy Die hochrothe goldlosung als reagens auf colloide, Fresenius Ztschr f analytische Chem. 40 697, 1901

<sup>52</sup> Zaloziecki Ueber den Eiweissgehalt der Cerebrospinalflussigkeit, Ztschr f Nervenhe 47 783, 1913

and is indicative of a more or less specific reaction on the part of certain tissues of the nervous system or of a decreased or altered permeability of the choroid plexus. While commonly a rather constant relationship exists between the various reactions in certain types of lesions of the nervous system yet it is amply demonstrated that any one of the reactions may be present when the others are absent, and that the type or degree of the reaction may vary widely from that of any other reaction. To illustrate in tabes dorsalis a typical laboratory report may read Nonne +, cells 40, colloidal gold 133 4432000, Wassermann +. But it is evident that the same substance is not responsible for all these findings, for any one or more of these tests may be positive and the others be negative.

Furthermore, none of these tests depends on a common provoking substance, for many conditions will cause increased albumin and globulin in the cerebrospinal fluid, the same is true of the varying degree of cellular increase, the colloidal gold curve and the complement fixation tests are more specific, but even here we find the colloidal gold curves of dementia paralytica and cerebrospinal syphilis occurring in cases of multiple sclerosis and brain abscess.

From the fact that these reactions can occur in diseases of different etiology, it is apparent that the reactions are dependent on various types of tissue change rather than on modified forms of the *Treponema pallidum*, as we might suppose if these reactions occurred only in syphilitic lesions of the central nervous system. It is possible, however, that various forms or fractions of the organism may tend to involve certain tissues more than others.

It is evident that a definite diagnosis should not be made on the presence of one of these reactions other than that any distinct abnormality of the cerebrospinal fluid indicates a pathologic condition of the central nervous system. One can understand that it would be possible to have a positive Wassermann reaction in the spinal fluid without definite syphilis of the nervous system, due, perhaps, to an altered permeability of the choroid plexus or to a high concentration of antibodies in the blood.

As Felton and Maxy have pointed out, "zonal" reactions are not specific and should not be designated by descriptive terms.

While emphasizing the nonspecificity of the color changes in the various dilutions it is our experience that they are of diagnostic value if corroborated by, or corroborative of, any other reactions or clinical findings. Thus, a reaction in zone I usually means dementia paralytica, in zone II, cerebrospinal syphilis or tabes dorsalis and in zone III, meningitis.

We had two interesting illustrations of this recently. A patient who had tabo-paresis, with clinical evidence of pachymeningitis hypertrophica cervicalis, gave definite color changes into zones II and III. The second patient was admitted to the hospital in a state of delirium with no history except that he had been sick a week or more. Well marked signs of meningitis were present and examination of the chest suggested the presence of pulmonary tuberculosis. The spinal fluid was under increased pressure and was perfectly clear. A diagnosis of tuberculous meningitis was made. No bacteria were found in the fluid on repeated examinations and the colloidal gold solution was almost completely reduced in all except the first dilution. This suggested a cerebrospinal syphilis in addition to the meningitis. This was confirmed by repeated positive blood and spinal fluid Wassermanns. Under antisymphilitic treatment the patient improved markedly and the meningitic symptoms cleared up largely.

Textbooks and observers frequently differ as to the cell count to be considered as pathologic, the most common view, however, being that any number below 10 is normal. Many writers feel that this is too high a limit. Kafka considers anything above 5 as pathologic. Dreyfus<sup>53</sup> gives the following classification: 1 to 5, normal, 6 to 9, doubtful, 10 to 20, slight pleocytosis, 21 to 50, moderate pleocytosis, and over 50 as a marked pleocytosis. Black and Vernes<sup>54</sup> believed that the count considered normal was too high, and from their own observations concluded that less than one lymphocyte was a normal count and that two or three lymphocytes should be considered as pathologic. Genoese<sup>55</sup> considers more than one lymphocyte distinctly pathologic.

In our series there was not a single count of over five cells in a nonsymphilitic or non-neurologic case, and the average was 1.6 cells in our normal spinal fluids. From this fact as well as the findings of others we believe that five should be the limit of a normal cell count.

The consensus of opinion seems to be that we have practically always a pleocytosis in syphilis of the central nervous system, but Mitchel, Darling and Newcomb,<sup>56</sup> making 300 counts on 34 patients, with untreated syphilis, in two weeks, found great variations in short intervals in every stage of the disease, either high or low counts appearing at any time in the disease, persisting for months, or chang-

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53 Dreyfus. *Die Methoden der Untersuchung des Liquor cerebrospinalis bei Syphilis*, Munchen med Wchnschr 59 2561, 1912.

54 Black and Vernes. *Les lymphocytes du liquide Cephalorachidiens normal*, Compt rend Soc de biol 75 231, 1918.

55 Genoese. *The Cerebrospinal Fluid During Malaria in Children*, Policlinico 26 737, 1919.

56 Mitchel, Darling and Newcomb. *Observations on Spinal Fluid Cell Count in Untreated Cases of Cerebrospinal Syphilis*, J Nerv & Ment Dis 41 686, 1914.



ing completely in intervals of only a few weeks. They also failed to find any parallelism between changes in the cell count and clinical symptoms.

Solomon and Koefod in a study of spinal fluid cellular content in cases of syphilis of the central nervous system after treatment found that the number of cells may vary greatly, changing from normal to high counts or from high to low counts within a few days. They conclude that the number of cells gives no definite information on duration, severity, or prognosis of the disease and is of no value in differentiating between cerebrospinal syphilis and dementia paralytica.

Lowrey in a study of what he terms "brain lues" reports the following results: 3 or 4 cells in four cases, from 5 to 10 cells in thirteen cases, from 11 to 25 cells in twenty cases, from 26 to 50 cells in twenty-six cases, from 51 to 100 cells in thirty-eight cases, and from 101 to 250 cells in twenty-seven cases, showing that an appreciable number of patients had low counts.

From a study of the repeated fluid examinations in treated and untreated cases we find a somewhat greater reduction of the number of cells in long treated than in untreated cases. There was, however, great variability in the counts at different times and the findings in general agree with those mentioned above.

The colloidal gold reaction, while requiring a careful technique, has been simplified by careful workers until it is easily within the reach of any routine laboratory. It is also unquestionably the most sensitive and valuable of the various tests used in a study of the spinal fluid. It does not usurp the place of any of the other tests nor make a careful neurologic examination unnecessary, but does have a definite and independent value, and no examination of the spinal fluid is complete without it.

As Fildes, Parnell and Maitland,<sup>57</sup> and Wile and Stokes<sup>58</sup> have pointed out, the spinal fluid may give evidence of involvement of the central nervous system early in the course of syphilitic infection. Since early treatment is of such vital importance in neurosyphilis, it is essential that in every case of general syphilis, especially with any signs of nervous system involvement, a complete study of the spinal fluid should be made as well as a careful neurologic examination.

On contemplating the large amount of literature on the subject one is impressed by the fact that the colloidal gold reaction has passed through the stage of experimentation with resulting over-expectation.

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<sup>57</sup> Fildes, Parnell and Maitland. Unsuspected Involvement of the Central Nervous System, *Arch Neurol & Psychiat* **1** 231 (Feb) 1919.

<sup>58</sup> Wile and Stokes. Involvement of the Nervous System During the Primary Stage of Syphilis, *J A M A* **64** 979 (March 20) 1915.

and exploitation, then the reactionary period of comparative neglect and indifference, and now has reached the intermediate and permanent stage of acceptance, occupying an independent position of its own and forming a necessary part of every routine laboratory spinal fluid analysis and careful neurologic examination. With Lange we believe that this reaction often determines the presence of an early and slight involvement of the nervous system and is, therefore, of great importance in early diagnosis, permitting of early treatment and thereby preventing or modifying severe syphilitic and "metasyphilitic" diseases of the central nervous system.

#### SUMMARY

1 The colloidal gold test is the most delicate of the routine spinal fluid reactions.

2 With careful technic and proper attention to neutrality successful colloidal gold solutions are within the reach of every laboratory worker.

3 It does not replace any other test but, on the other hand, is of independent value.

4 It is of especial importance in the early diagnosis of neurosyphilis.

5 The various curves are not specific but are of great diagnostic value in conjunction with other clinical and laboratory findings.

6 A colloidal gold curve may be obtained with or without other positive findings after provocative treatment.

7 The colloidal gold curve does not parallel clinical signs nor give definite evidence of improvement under treatment.

8 Patients with no involvement of the central nervous system or who are nonsyphilitic give no colloidal gold curve.

9 Clear-cut clinical cases of tabes dorsalis may show all the spinal fluid reactions negative both before and after treatment.

10 A curve in zone III with a negative cell count and negative or faintly positive globulin is strongly suggestive of a brain or cord tumor or myelitis.

11 Curves in zones I and II may be found in nonsyphilitic conditions, such as multiple sclerosis and brain abscess.

12 A cell count above five is pathologic, but the cell count is of no value in indicating duration or severity of the process or improvement.

13 This reaction should be included in every spinal fluid analysis and neurologic examination as well as in all cases of general syphilis.

# AN ANALYSIS OF THE SPREAD OF THE EXCITATION WAVE IN THE HUMAN VENTRICLE

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We are now in the possession of a method and sufficient anatomic and physiologic information for a detailed and fairly accurate analysis of the normal and pathologic spread of the excitation wave in the human heart. Such an analysis will help to clarify some of our somewhat hazy and even inaccurate ideas as to the causes of the form of the normal and pathologic electrocardiogram. Using the method of the equilateral triangle devised by Einthoven,<sup>1</sup> I attempted an analysis of the propagation of the wave of electronegativity in the human heart in 1914.<sup>2</sup> This paper has for its purpose the more extended introduction of the method among American clinicians and a revision of some of the ideas developed in that paper. The work of Rothschild and Lewis<sup>3</sup> on the velocity of conduction in the heart muscle has been especially helpful in revising our ideas as to the propagation of the electronegative wave in the heart.

Let us first consider the propagation of the wave of electronegativity in a straight muscle cylinder (Fig 1, *A-B*) immersed in a physiologic salt solution contained in a glass cylinder (Fig 1, *C-D*). The two ends of this glass cylinder are connected by nonpolarizable electrodes with a string galvanometer. If the muscle is stimulated at *X* this point becomes electronegative with respect to the rest of the muscle mass, currents of electricity flow in the tissue juices surrounding the muscle fibers and in the physiologic salt solution in which it is immersed. There is a difference of potential between the ends *C* and *D* of the glass cylinder. Just as the end *B* of the muscle cylinder is more negative than the end *A*, so also the end *D* of the glass cylinder is more negative than the end *C*, and a current of positive electricity will run in the galvanometer from *C* to *D*, conversely, the direction of the galvanometer deflection will indicate to the observer which end of the muscle has been thrown into the state of excitation. From *x* the excitation process will spread toward both ends with equal velocity. The end *B* will receive the electronegative wave first. At this moment the galvanometer will show the maximum deflection in the original direction. The wave of electronegativity continues its journey toward

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1 Einthoven. Fahr u. de Waart. Arch f d ges Physiol **150** 275, 1913

2 Fahr and Weber. Deutsch Arch f klin Med **117** 361, 1915

3 Lewis and Rothschild. Phil Trans, B, **206** 181, 1915

*A*, while the electronegativity is dying out at *B*. Finally, the excitation process reaches the end *A*, this point now has its maximum negativity, whereas the point *B* has lost its negativity or is losing it in the normal process of return to the original state. At this moment the point *C* of the glass cylinder is more negative than the point *D*, an electric current runs from *D* to *C* through the galvanometer which shows a deflection in the opposite direction corresponding to the reversal of the direction of the potential difference in the muscle cylinder *A-B* and the glass cylinder *C-D*.

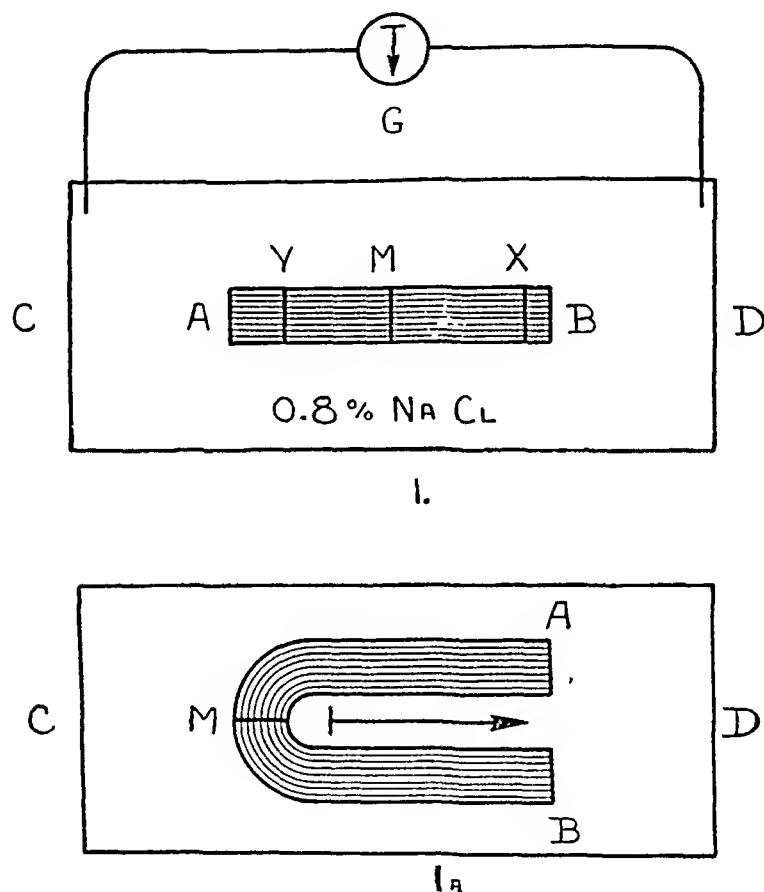


Fig 1—Diagrammatic representation of a thin muscle cylinder immersed in physiologic salt solution contained in a very large cylindrical glass vessel with one galvanometer lead

We have traced the development of a diphasic current in a muscle cylinder stimulated near one end *B* with its spread throughout the muscle mass and have followed the curve described by the string galvanometer in this simple case. If we stimulate the muscle at *y*, the end *A* of the muscle will be more negative than the end *B*, the end *C* more negative than the end *D*, and the current will run from *D* to *C* through the galvanometer indicating to the observer that the muscle is in a state of excitation at a point nearer to its *A* end than its *B* end.

It is necessary to consider the case when the muscle cylinder is stimulated at its center *m*. In this case the electronegative process starts at *m* and travels with equal velocity toward both ends. The ends *A* and *B* will have synchronously the same electrical potentials as the excitation process approaches them. There will be no difference of potential between *A* and *B*, and correspondingly no difference of potential between *C* and *D*. The galvanometer will in this case give no indication of activity in the muscle cylinder. The observer at the galvanometer will receive no indication that an excitation process has started at *m* and spread to both ends.

In the same way if both ends *A* and *B* are thrown into a state of excitation at the same moment, and in consequence both ends become electronegative in respect to points on the muscle near them, then *A* and *B* have equal potentials, in consequence, there will be no difference of potential between *C* and *D*, and the galvanometer will not indicate that there is activity in the muscle, despite the fact that both ends of the muscle mass are in excitation.

There is one more elementary case to be considered. The muscle cylinder is bent at *m* so that the ends *A* and *B* are next to one another, and this V-shaped muscle mass is immersed in the cylinder *C-D* in such a way that the ends *B* and *A* are toward *D*, and the middle *m* lies toward *C* (Fig 1, *A*). If the muscle is now stimulated at *m*, its middle point, we get a potential difference between *m* and *A*, and between *m* and *B* such that both *A* and *B* are positive to *m*. If we make use of an arrow to indicate the direction of a potential difference, the head indicating positivity and the tail negativity, the arrow in this case will point from *C* toward *D*. *D* is more positive than *C*, and a current passes through the galvanometer from *D* to *C*. The observer noting the direction of the deflection of the galvanometer can thereby determine that the portion of the muscle mass toward *C* is negative in respect to that portion toward *D*. In other words, he can deduce that a portion of muscle more toward *m* than toward *A* and *B* has been thrown into activity. By following the curve of the deflection of the galvanometer he can follow the spread of the activity from *m* toward *A* and *B*, and determine very closely the moment when *A* and *B* are thrown into activity, for at this moment the direction of the galvanometer deflection is opposite and reaches its maximum. Vice versa, if both points *A* and *B* are stimulated and the excitation process spreads toward *m*, the curve of the galvanometer deflection is exactly the reverse of the preceding curve. If *A* alone is first stimulated we have a potential difference such that the end *D* is negative to the end *C*. As the wave of electronegativity proceeds toward *m* the direction of the potential difference changes. When *m* is negative the ends *A*

and  $B$  are positive and the arrow points toward  $D$ . As the excitation wave spreads further along the muscle it finally approaches  $B$ , and when it arrives here  $B$  is negative to  $m$  and  $D$  is negative to  $C$  and the direction of the potential difference in the salt solution is again changed, that is, the arrow points toward  $C$ .

It is possible to twist our schematic muscle cylinder into innumerable shapes and to consider each of these cases as we have considered the above few in detail. But the moment we begin to twist the muscle cylinder into various shapes the electronegative wave travels at certain points in directions at right angles to the direction  $C-D$ . We shall, therefore, next consider a few simple cases of propagation of the excitation process in a muscle mass immersed in a flat rectangular receptacle containing physiologic sodium chlorid solution (Fig 2).

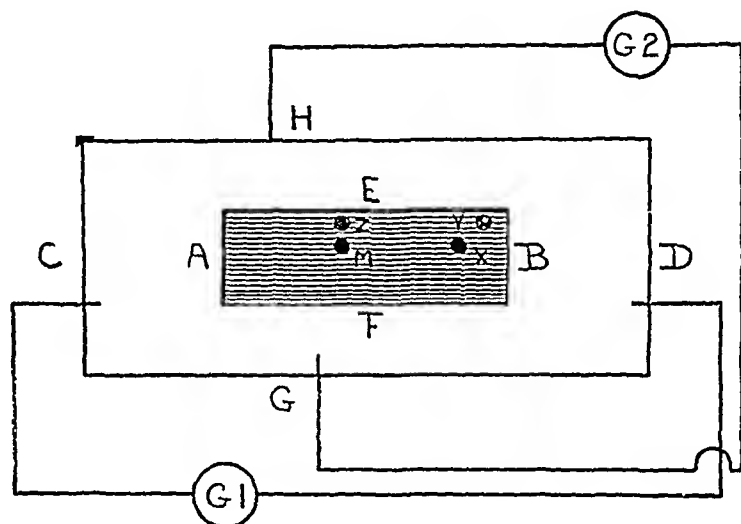


Fig 2—Diagrammatic representation of a flat muscle sheet immersed in a flat rectangular vessel of salt solution with two galvanometer leads

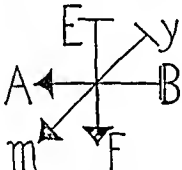
$A-B-E-F$  is the muscle mass.  $C-D-H-G$  is the glass vessel filled with the physiologic sodium chlorid solution. One galvanometer ( $G1$ ) is connected to the ends  $C$  and  $D$ , thus we shall call lead I. The other galvanometer is connected to the sides  $H$  and  $G$ . We shall call this lead II. If the muscle is excited at  $x$ , the electronegativity is first present at  $x$ , the rest of the muscle is positive to  $x$ . The end  $B$  is less positive than the end  $A$ , therefore, as far as these ends are concerned there is a potential difference in the muscle of such direction that an arrow indicating the direction of potential in the muscle fiber will have the direction  $A \leftarrow B$  if the head indicates positivity and the tail negativity.

As  $x$  is symmetrically placed with respect to the sides  $E$  and  $F$  there will be no difference of potential between them, and, therefore, no potential difference between  $H$  and  $G$  and the galvanometer 2 will

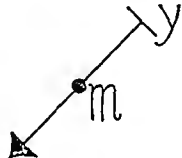
indicate no activity. The galvanometer 1 will be deflected in a direction indicating a potential difference between  $C$  and  $D$  in such a direction that the current runs from  $C$  to  $D$ . The observer of the galvanometers will see a deflection in lead I and none in lead II, and will conclude that there is a point of activity in the muscle located symmetrically to  $E$  and  $F$  and nearer  $B$  than  $A$ . He can follow the spread of the excitation process throughout the muscle.

If we stimulate the muscle at  $z$  we get no difference of potential between  $A$  and  $B$  because they are equidistant and symmetrically placed with respect to  $z$ . There will be a potential difference between  $E$  and  $F$  of directions  $\downarrow_F^E$  because  $z$  is nearer  $E$ . Galvanometer 1 will show no deflection. Galvanometer 2 will be deflected in a direction indicating current passing from  $G$  to  $H$ , and the observer will conclude from the galvanometer deflections that the muscle is active at a point nearer  $E$  than  $F$ , and equidistant from  $A$  and  $B$ .

If the muscle is stimulated to activity at  $y$ ,  $B$  is negative to  $A$  because  $y$  is nearer  $B$ , and  $E$  is negative to  $F$ , for  $y$  is nearer the side  $E$  than the side  $F$ . There will be a potential difference in the muscle

whose direction  $y m$   can be resolved into the two com-

ponents  $EF$  and  $AB$ . The galvanometers are deflected in such a way that lead I indicates  $E$  negative to  $F$  and lead II indicates  $B$  negative to  $A$ . The observer must combine the two potential differences at right angles to one another in order to get the resultant potential difference. This resultant will indicate to him the point at which the muscle is in activity. For if he gets his resultant and draws it into a

figure shaped like  the muscle, drawing it in such a

way that the arrow passes through the center of gravity  $m$ , the negative end  $y$  will point toward that area of muscle which is in a state of activity.

If  $m$ , the center of gravity, is excited, this point is negative with respect to all others, but as the distribution of potential is symmetrical, and as  $A$  and  $B$  are equidistant and  $E$  and  $F$  are equidistant from  $m$ , there will be no potential difference between  $E$  and  $F$  or between  $A$  and  $B$ . There is no resultant potential difference in the whole mass. It must be remembered that there is a potential difference between  $A$  and  $m$  but as this is equal and opposite to the potential difference

between  $B$  and  $m$  they neutralize one another as far as the ends  $C$  and  $D$  are concerned. And although there is a potential difference  $\uparrow_m^E mE$  and also one  $\downarrow_x^m mF$  these two neutralize one another. There is no potential difference  $EF$ . Neither galvanometer is deflected. The observer cannot know whether the muscle is inactive or whether there is activity at its center of gravity.

If both  $z$  and  $x$  are active at the same moment we get two potential

differences  $A \leftarrow \begin{array}{c} E \\ \nearrow y \\ \searrow m \\ \downarrow F \end{array} B$   $EF$  and  $BA$  which combine to a resultant  $ym$ .

Both galvanometers 1 and 2 are deflected. One indicates negativity at  $E$  the other at  $B$ . The observer can not tell whether he has a resultant potential difference due to stimulation at two points  $z$  and  $x$ , or a potential difference due to stimulation only at a point near  $y$ . It is true that the potential difference due to stimulation at the two points  $z$  and  $x$  is of greater magnitude than that due to stimulation at one point,  $y$ , only. This might help him decide as to the exact point of origin of the stimulus, but it is very easy for the reader to see that as soon as we have to do with the origin and spread of electronegativity in a muscle mass extending in two dimensions of space, with two galvanometer leads, it becomes impossible to determine more than the general direction of a resultant potential difference and its magnitude. We must call in other data to aid us in finding the point of origin and in following the spread of the excitation process. In the heart, for example, many points are stimulated nearly simultaneously and the spread is very rapid. It is only by following the change in direction and magnitude of the resultant potential difference, combined with our knowledge of the architecture of the specific conducting system, that we can analyze the path of the spread in the human ventricle.

The above consideration of certain elementary cases is sufficient to show the reader that the problem of determining the points of a muscle which are in a state of excitation from galvanometer leads applied to points external to the muscle is not an easy one and that we cannot always determine each individual point. We can determine a resultant potential difference by geometrical construction, following the method of combining vectors. If the arrow representing the direction and magnitude of this resultant vector is drawn through the center of gravity of the geometrical figure representing the object, its tail will point in the direction of the center of electronegative mass.

We desire to impress the reader with the fact that it is impossible to determine anything other than the magnitude and direction of this resultant vector of potential difference from the deflections of the



galvanometers both in these simple cases and in the more complicated case of the distribution of electronegativity in the human heart immersed in the conducting substances of the human body

We have been considering potential differences in one or two dimensional muscles up to the present. The heart is an object of three dimensions. The three leads of electrocardiography lie in the frontal plane and therefore they only indicate potential differences in this plane or the projection upon this plane of potential differences lying in other planes of space. In other words, the electrocardiogram is a frontal projection of electrical distribution in the heart just as the percussion figure, the orthodiagram or the roentgenogram of the heart is a frontal projection of the mass distribution in the heart. These projections appear sufficient at present for practical purposes.

The ventricle is a complicated system of twisted muscle fibers immersed in a conducting medium less simple than our cylinder of physiologic sodium chlorid solution. Moreover, the excitation process in the heart does not start at one point and spread by muscle conduction, but the excitation process starts nearly simultaneously at various points on the endocardial surface, spreading from here outward by muscle conduction<sup>4</sup>. And finally the electrocardiogram is recorded from leads I, II and III, or from right arm and left arm, right arm and left leg and left arm and left leg. We shall, therefore, find it necessary to adopt a schematization of the human body as an electric conductor, and to make use of our knowledge of the architecture of the His-Tawara system and its terminal arborizations in order to follow approximately the spread of the excitation process in the heart.

Einthoven<sup>1</sup> has given us a schema by means of which it is possible to determine the exact direction of the potential difference in the human heart from three synchronous leads at any time in a given heart cycle. I have modified the method slightly so that it is possible to determine graphically from any two leads the exact direction of the potential difference in the heart at any desired moment. By following the changes in direction and magnitude of the vector representing the potential difference in the heart, it is possible to follow the spread of electronegativity throughout the heart.

Einthoven was aided in his search for a simple geometric form on which to base a schema of the distribution of potential in the human body by the fact that the potential differences between the right leg and the left leg are of negligible magnitude in electrocardiography so that the two legs may be regarded as one isoelectric point<sup>5</sup>. He assumed that the distribution of potential on the surface of the body

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4 Lewis and Rothschild. *Phil Trans B* **206** 181, 1915

5 Einthoven. *Le Telecardiogramme*, *Arch internat de Physiol* **4** 149, 1907

when an electrical tension is present in the heart is similar to the distribution of potential in an equilateral triangle of good conducting material when a potential difference has been developed very near to its geometrical center. Right arm, left arm and left foot (or right foot) represent the corners of the triangle. If we accept this assumption of Einthoven's as representing the actual conditions sufficiently accurately, it is possible to devise a method whereby we can tell just what direction the potential difference in the heart has at any given moment, and also to determine a derived value of the electromotive force in the heart, the so-called "manifest value," a value which bears a constant relation to the actual potential difference in the heart and which changes in value in exact ratio to the change in magnitude of the actual potential difference produced in the heart during each cardiac cycle.

The distribution of potential in an equilateral triangle is very simple if a potential difference has been produced at two points lying very close to its geometrical center. If we lead off from the three corners of the triangle, then the potential differences between any pair of corners is to the potential difference between any other pair of corners as the projection of a line having the direction of the potential difference at the center on the side of the triangle lying between the first two corners is to the projection on the side of the triangle between the second pair of corners, for example, in Figure 3, if we produce a potential difference having the direction  $A \rightarrow B$  in the middle of the equilateral triangle  $RLF$ , then the potential difference between  $R$  and  $L$  is to the potential difference between  $R$  and  $F$  as the length of the line  $A_1 B_1$  is to the length of the line  $A_2 B_2$ .

We can find the real direction of the electrical tension in the heart at any phase in its activity from the synchronous heights of the electrocardiograms in two leads, and we can determine the magnitude of the potential difference in the heart as manifested at the body surface at this moment, if Einthoven's equilateral triangle assumption is correct. If we examine the equilateral triangle (Fig. 3) we can see that the lines  $AC$  and  $Ad$  are parallel and equal to the lines  $A_1 B_1$  and  $A_2 B_2$ , and that the perpendiculars dropped from their ends cut one another in  $B$ . This rule holds for all possible directions of  $AB$ . If we draw (Fig. 4) two lines enclosing an angle of 60 degrees between them and make the ratio of the lengths of these lines the same as the ratio of the potential differences in lead I and lead II, let perpendiculars fall from their ends  $D$  and  $C$ , and connect the point of intersection  $B$  with  $A$ , then  $AB$  has the direction of the potential difference in the center of the equilateral triangle, therefore in the heart. The length of the line  $AB$  corresponds to the "manifest value" of the actual potential

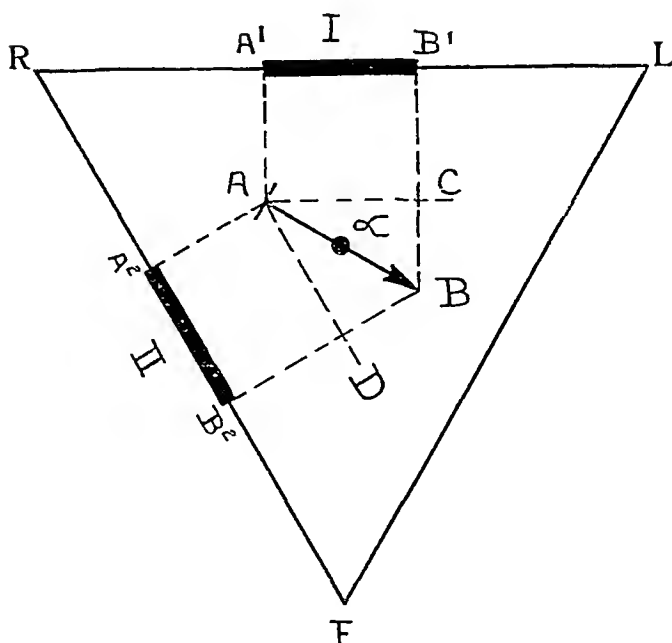


Fig 3—The equilateral triangle scheme R= right hand L= left hand F= foot AB= vector of potential difference in heart  $A_1B_1$ = projection of AB on RL Corresponds in length to the relative value of lead I  $A_2B_2$ = projection of AB on RF Corresponds in length to the relative value of Lead II

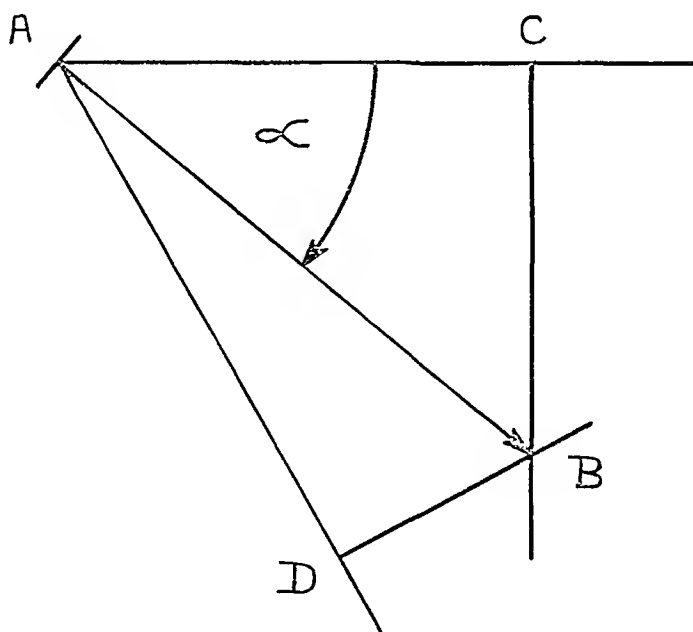


Fig 4—Construction of direction and "manifest value" of a potential difference in the heart AC corresponds in length to Lead I AD corresponds in length to Lead II AB corresponds in length and direction to "manifest value" of heart potential

difference present in the heart, for Einthoven defines the "manifest value" of the potential difference actually present in the heart as the value which is found in one of three leads when the direction of the current between the leading off points is parallel to the direction of the potential difference in the heart. The length of the line  $AB$  must correspond to the "manifest value" according to the above definition because the projection of  $AB$  upon a side parallel to it is exactly equal to  $AB$ . Or, perhaps, it will be clearer if we think of the potential difference at the center of the equilateral triangle with the direction  $AB$  and with a value for lead I  $= A_1 B_1$  gradually turning into a position parallel to  $RL$ . In this case the value of lead I will come to equal the length  $AB$ . The "manifest value" is a very important magnitude. In each person there is a definite and constant relation between the actual potential differences existing at the points of production in the heart muscle and the "manifest value" as determined above. We shall probably never learn the actual value of the potential differences developed in the heart muscle. The values obtained by placing electrodes directly on the heart are just as much derived values as those obtained by leading off from the limbs. The electrical potentials present at two points of the heart's surface are due to the algebraically added potentials produced by points of activity throughout the whole heart in exactly the same sense as the electrical potentials present in the limbs are due to the algebraically added potentials produced by these same points of activity. The "manifest value" has a constant relation to the actual potential difference in the heart and therefore may be used as a measure of the actual potential difference. The actual potential difference in the heart varies from moment to moment throughout the heart cycle according to exactly the same curve as the "manifest value". To avoid any misunderstanding it is necessary to state here that the "manifest value" as determined above is the frontal projection "manifest value". If the heart turns about an axis, the frontal plane projection will vary if the axis of rotation is not perpendicular to this plane. The determination of the "manifest value" is just as important in analyzing the spread of the excitation wave in the heart as the determination of the direction of the potential difference.

The angle between the direction of the actual difference in the heart and the horizontal line connecting the points of attachment of the two arms to the body has been called  $\alpha$  by Einthoven. It is the angle between  $AB$  and  $AC$  in Figures 3 and 4.  $\alpha$  is defined positive for the first 180 degrees in clockwise rotation from the direction of  $AC$ , and is defined negative for the first 180 degrees in anticlockwise direction from  $AC$ .

The procedure of the author for finding the direction of the potential difference in the heart and its "manifest value" is as follows. An angle of 60 degrees is constructed. Along the horizontal side of the angle a distance equal in centimeters to the value of lead I in tenths of millivolts is laid off. Along the other side of the angle a distance is laid off whose length in centimeters equals the synchronous value of lead II in tenths of millivolts. Perpendiculars are dropped from the end of these lines. The point of intersection is connected with the vertex of the angle. The length of this line in centimeters gives the potential difference corresponding to the "manifest value" for this moment in the cardiac cycle, the direction of this line gives the direction of the resultant electromotive force present in the heart at this moment and the angle formed by this line with the horizontal line is the angle  $\alpha$ .

The schema of the equilateral triangle was only an assumption when propounded by Einthoven. In 1914 I carried out some experiments in the clinical laboratory of the department of internal medicine of the University of Giessen with Professor Weber which demonstrated that the Einthoven assumption was accurate enough for purposes of electrocardiography. Electrodes were placed in the heart of bodies which were waiting for necropsy. The electrodes were isolated, except where they entered the heart. Potential differences were developed in the heart by means of a storage battery connected to the electrodes. By means of two string galvanometers the potential differences of lead I and lead II were recorded. The electrodes were given various positions in the heart so as to produce various directions of potential difference in the heart. These directions were determined for each position of the electrodes and the angle  $\alpha$  thus measured compared with the angle  $\alpha$  constructed from leads I and II by our method. There was usually an agreement of better than 10 degrees between measured and constructed directions of the potential difference in the heart. In one case the measured and constructed direction of potential differed by about 20 degrees. These experiments showed that Einthoven's schema of the equilateral triangle is apparently accurate to  $\pm 10$  degrees, an accuracy sufficient for practical purposes. These experiments were carried out on only two cadavers, but we believe that they demonstrated for the first time that Einthoven's schema of the equilateral triangle is apparently accurate to  $\pm 10$  degrees. We can, therefore, make use of the method for determining the direction and "manifest value" of the electromotive force developed in the heart during the heart's activity.

It is necessary to emphasize that only synchronous points in the three leads may be used for the construction. It is not permissible to use the peaks of the *R* waves in two leads. A difference of 0.01 second in the phase of the ordinates may cause an error of 60 degrees in the determination of the direction of potential in the heart. The *R* peaks in the various leads are almost never synchronous as the reader will immediately appreciate when he considers that the *R* peaks repre-

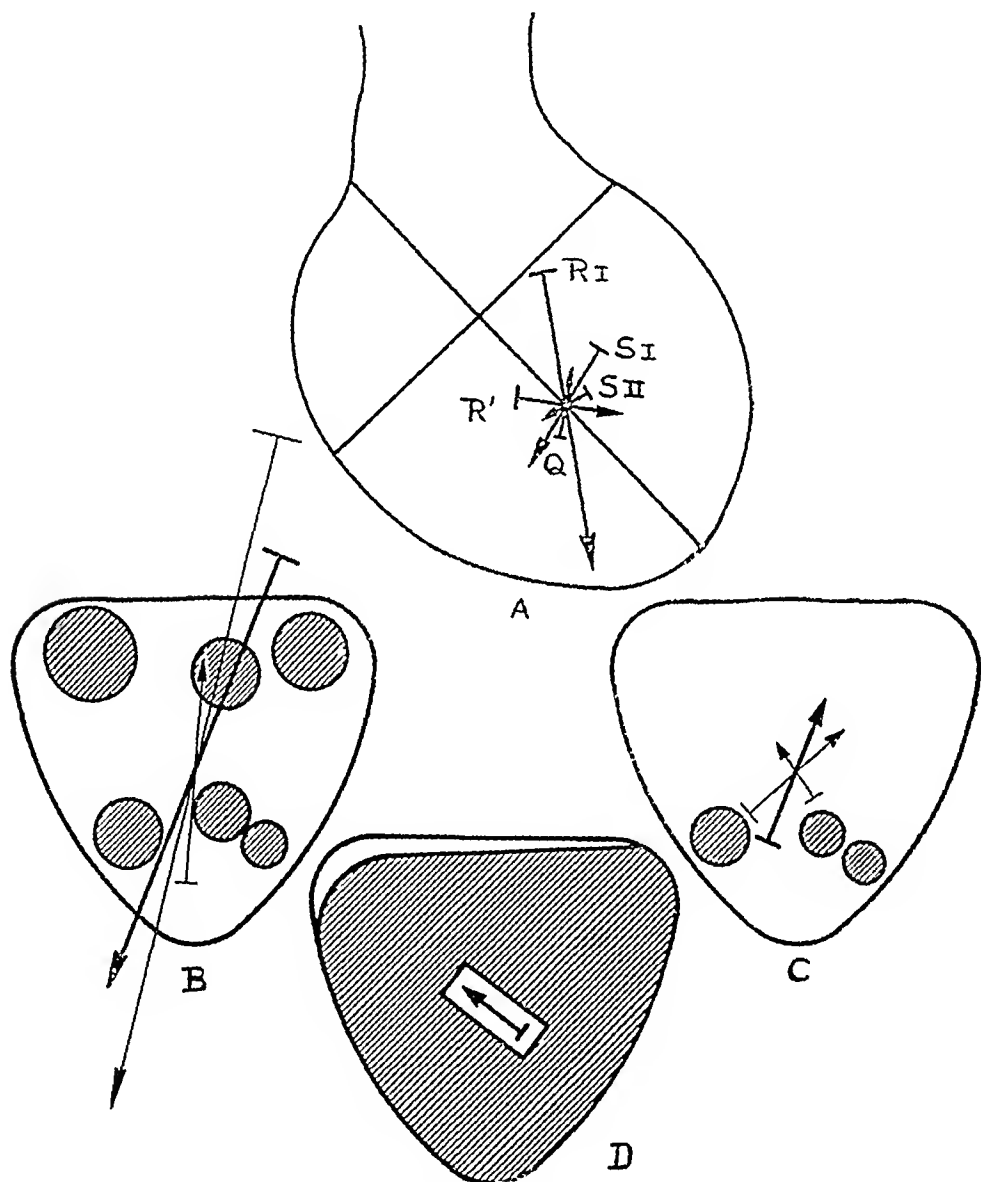


Fig 5—A Orthodiagram of normal heart with vectors of potential corresponding to various points of electrocardiogram. B Direction of potential difference when all the subendocardial area of apex is electronegative and most of the basal subendocardial area is negative at time of R peak. C Direction of potential difference when areas about three papillaries are electronegative at time of Q wave, the right papillary in this case having received the negative wave first because of shorter path. D Direction of potential when all of the heart muscle is negative (both Purkinje and ordinary heart muscle) except a small volume of muscle about the right base.

sent the maximum projections of a rotating vector of potential upon three lines whose directions vary by 60 degrees. It is often of advantage to use leads I and III or leads II and III instead of leads I and II in constructing the vectors of potential difference in the heart. A glance at Figure 3 will show how the construction is made in each of these cases.

Figure 5 is the orthodiagram of a normal heart in which arrows have been drawn to represent the direction and "manifest value" of the electromotive force in the ventricle at five different phases of the ventricular systole. These arrows were constructed according to my method and drawn through a point in the orthodiagram assumed to be close to the center of gravity of the ventricular mass. The arrow marked  $Q$  was constructed from synchronous points on the two electrocardiograms corresponding to the apex of the  $Q$  wave. The arrow  $R^1$  represents the direction and "manifest value" of the potential difference in the heart 0.01 second later and the arrow  $R_1$  represents the direction and magnitude corresponding to the peak of the  $R_1$  wave about 0.02 second after the  $Q$  wave. The arrow  $S_1$  was constructed for a period corresponding to the apex of the  $S$  wave in lead I nearly 0.02 second after the  $R_1$  peak. The apex of the  $S$  wave in lead II was reached somewhat later, at which time the vector representing the direction and "manifest value" of the electrical tension in the heart is the arrow  $S_{II}$ . These arrows are sufficient to give us an idea of how the excitation wave spread over the ventricle of this heart. The first signs of ventricular negativity is the  $Q$  wave. This is the moment when the excitation process coming down the His-Tawara bundle shoots into the ventricles in areas of the subendocardium close to the three papillary muscles, the right papillary and the anterior and posterior of the left ventricle. The direction of this arrow indicates that the preponderance of negativity at this moment is on the right side and more toward the apex than the base of the ventricles. The distance traveled by the negative wave along the right bundle branch to the point at which it spreads out in the subendocardial layers of the right ventricle is less than the distance traveled along the anterior papillary and the posterior papillary branches of the left ventricle to the points at which these branches merge into the subendocardial layers of the left ventricle. The right ventricle is negative a short time before the left.

Figure 5<sup>c</sup> is a graphical representation of the frontal projection of a heart and the areas of excitation at the period of a heart's cycle represented by the  $Q$  wave. In the right ventricle there is an area somewhat larger than either of the areas in the left ventricle. Assuming that the velocity of the excitation wave in the subendocardial

layers is two and one half meters and that the path to the two papillary muscles in the left ventricle is about one centimeter longer than to the papillary in the right ventricle, the size of the circles represents exactly the size of the areas in excitation about the right papillary and the two left papillary muscles. The two short arrows represent the vectors of potential for the two ventricles and the long arrow represents the resultant potential difference in the heart. The apical subendocardial layer in the right ventricle is practically all in excitation at this moment. In about 0.004 second more the whole of the apical subendocardial layer in the left ventricle will be saturated with negativity.

About 0.01 second later the "manifest value" has increased and the vector has rotated into position  $R^1$ . This could only be brought about by an increase in negativity at the bases and an increase in the spread of the negativity in the left ventricle. In other words, the negativity is spreading out in the subendocardial layers of the conducting system toward the base and in the left ventricle the lag due to the increased length of path is being overcome. About 0.01 second later the arrow indicating the direction and "manifest value" of the potential difference in the heart has the direction and length  $R_1$ . In other words, electronegativity has increased more rapidly at the base than the apex, and more rapidly in the left ventricle than in the right, the center of electrical mass is in the base of the ventricles a little more toward the left side than the right side of the heart.

Figure 5<sup>b</sup> is a graphical approximation of the relation of the excited or negative areas in the heart at a point in the heart cycle represented by the  $R_1$  peak. The subendocardial apical areas are all negative now and the basal areas of the subendocardium in both ventricles are also nearly saturated with negativity. The amount in the left ventricles predominates slightly. The  $R_1$  peak represents a point in the cardiac cycle about 0.03 second after the beginning of negativity in the ventricles. The path to the left ventricles is perhaps slightly longer. If we assume it to be one centimeter longer, the negativity gets into the left ventricle about 0.004 second after it has reached the right ventricle. But the spread toward the bases of the ventricles has an advantage in the left ventricle, namely, there is a spread from two separate areas, the areas about the two papillary muscles of the left ventricle. In some cases this advantage in accelerating the spread of the negative wave in the left ventricle will more than overcome the disadvantage due to the negativity reaching the left ventricle a very short time after it reaches the right ventricle. This may be the explanation of the direction of the vector  $R_1$ . The size of the circles in this figure were determined by considering the heart to be a very simple geometric figure



and using orthodiagraphic dimensions for calculating the size of the internal areas of the ventricles. Of course the figures are merely graphical schemes to aid the imagination. It still remains for some one to make geometrical studies of the form and dimensions of the ventricles and their topographical relation in space.

The reader who has followed the reasoning employed in the discussion of the elementary cases in the first part of this paper will inquire how the base can become more negative than the apex if the negativity first reached an area nearer the apex than the base. There are a number of possible explanations for this. The center of gravity is determined by the distribution of muscle mass in space. The heart can be likened to a hollow cone with a partition in it. If the walls of this hollow cone were of equal thickness on both sides of the partition, and if the partition lay in the sagittal plane of the body it would be a simple matter to find the center of gravity by mathematical procedures. As it is, we can only say about where the center of gravity lies. It must be somewhere between the upper third and lower half of the septum and toward the left side of the septum. A plane passed through the center of gravity parallel to the base will divide the heart into two muscle masses which, when negative, gives rise to potential differences of equal "manifest value" and opposite direction. Because of the geometrical form of the heart, the area of the subendocardium corresponding to the apical muscle mass will be smaller than the area of the subendocardium corresponding to the basal muscle mass.

The excitation wave has a velocity in the subendocardial specific conducting layers which is from five to ten times the velocity in the heart muscle fibers themselves<sup>3</sup>. The excitation process enters the apical side of the subendocardium first, causing preponderance of apical negativity, and it spreads throughout the apical subendocardial layer at a velocity of from two and one half to three meters per second. At the same time it is spreading toward the base at the same rate. The whole of the subendocardial apical area is negative first, and from here the excitation process travels into the real muscle fibers. But it spreads here at a very slow rate, and very probably there is also a short pause for the transition so that in a very short period of time the whole of the basal subendocardial layer is negative, and as this area is larger than the apical area there is more electronegativity at the base than apex.

The *R* peak would, therefore, indicate approximately the end of the spread of excitation on the inside of the heart. From this point on, the electronegativity spreads from within outward. About 0.015 or 0.02 second after the *R* peak the *S<sub>I</sub>* peak is reached. The arrow *S<sub>I</sub>* indicates the "manifest value" and direction of potential at this

moment The rotation of the vector from  $R_I$  to  $S_I$  can only be brought about by an increase in apical negativity of such magnitude that the base is now only a very little more negative than the apex Just how the apical negativity increases so much more rapidly than the basal at this point can only be inferred One assumption is that after the subendocardial layers become negative there is a slight pause in the spread of the excitation process from the peculiar Purkinje fibers into the heart muscle fibers This would be analogous to what always happens when the excitation process passes from one kind of tissue into another If this assumption is in accordance with the facts, then as the apical subendocardial layer of specific conducting fibers became negative a little sooner than the basal subendocardial area, the excitation process would pass over into the ordinary muscle fibers of the apex about as far ahead of the excitation process in the ordinary fibers at the base as the excitation process in the apical subendocardial area was ahead of the excitation process in the Purkinje system at the base This assumption, which appears plausible, would explain very nicely the rotation of our vector toward the apex and the production of the S wave in lead II If our assumption is correct, the peak of the  $R$  marks the beginning of the spread of the excitation process in the real heart muscle fibers and in areas nearer the apex than the base of the heart

The arrow  $S_{II}$  is the vector for a point in the heart cycle about 0.01 second after  $S_I$  The arrow has rotated still farther toward the apex At this point the "manifest value" is very small, showing that nearly all of the heart muscle is negative or excited with just a little more apical basal muscle in excitation With the spread of the negativity to the remaining basal portions the spread of the excitation process is complete The whole heart is negative and the resultant potential difference in the heart is zero The galvanometers indicate no current

We have attempted a graphical representation of the excited heart muscle in Figure 5<sup>d</sup> corresponding to the  $S_{II}$  peak A small rim of heart muscle toward the base a little larger on the right side is still unexcited An explanation for this can be found in the fact that the path of conduction in the subendocardium to the base is the longest path, and therefore the heart muscle fibers here receive their negativity from the Purkinje system last We have assumed that the negative process in the basal subendocardial areas of the Purkinje system on the right side of some hearts lags a little behind the area on the left side because the negativity spreads from two points in the left ventricle Because of this the spread of negativity in the uppermost portions of the basal heart muscle on the right will lag a little behind the spread on the left side in these hearts

This analysis of the spread of the electronegative wave in the heart is in good accord with the known facts of the physiology of the heart. Garten<sup>6</sup> has shown that if the intraventricular pressure in the left ventricle of the dog is recorded with a very sensitive manometer of extremely slight inertia and great speed of reaction,<sup>7</sup> the first indication of pressure development in the left ventricle comes about 0.025 second after the beginning of the ventricular electrocardiogram and just before or just after the peak of the *R*. The pressure developed is at first very slight and becomes more marked farther down the catacrotic limb of the *R*. The maximum of intraventricular pressure is reached very shortly after the *QRS* group is complete. These curves of Garten suggest that small portions of the heart muscle are in contraction 0.015 second after the peak of the *Q* is reached and just before or at the *R* peak, and that the greater part of the heart muscle is in contraction by the time the *SII* peak is reached and before the end of the *QRS* group. The small "initial vibrations" of the first heart sound also appear about 0.03 second after the beginning of the ventricular electrocardiogram and before the *R* peak or just after the *R* peak.<sup>8</sup> The large vibrations of the first heart sound comes about 0.04 second after the beginning of the ventricular electrocardiogram, or about 0.01 second after the *R* peak and before the *SII* peak.

The early slow and slight rise in Garten's intraventricular pressure curves and the "initial vibrations" of the first heart sound curves are best explained as due to the contraction of the papillary muscles. These muscles receive their excitation before the rest of the heart muscle, during the *Q* wave period and as the contraction of the heart muscle begins not later than 0.004 second after the electronegative wave reaches it,<sup>9</sup> the papillary muscles are probably well in contraction 0.03 second after the beginning of the ventricular electrocardiogram. Using 400 centimeters per second as the velocity of the propagation of the negative process in the ordinary heart muscle fibers, we calculate that the greater part of the papillary muscles must be in contraction 0.03 second after the electronegative process reaches their bases. All the data at hand therefore agree very well with our interpretation that the *Q* wave represents the spread of the excitation process in the subendocardial Purkinje system of the apices.

The anacrotic limb of the *R* wave starts before the initial vibrations

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6 Garten. *Ztschr f Biolog* 66 23, 1915

7 The period of these manometers is only 0.003 second

8 Bull. Quart. J. Exper. Physiol. 4 289, 1911. Fahr. Heart 4 147, 1912

9 Kahn. Arch. f. d. ges. Physiol. 132 209, 1910. Garten. Loc. cit.

or the earliest indication of pressure development in the ventricles. The beginning of the *R* wave, therefore, does not represent the negativity of the ordinary muscle fibers of the papillary muscles to any great extent. It must represent some other process. The direction of the vector of potential indicates that the process is spreading toward the base of the heart. The anacrotic limb of the *R* is very probably associated with the spread of the negative process in the subendocardial Purkinje system toward the bases of the heart. Of course, there is negativity in the ordinary muscle fibers of the papillaries before the *R* peak is reached. But the papillaries are attached at points not far below the center of mass of the heart and their upper end extends toward the bases. When all parts of the papillary muscles are negative, the total effect on the direction of potential in the heart will be insufficient to neutralize the effect of the preponderance of subendocardial basal negativity.

The large vibrations of the first heart sound and the sharp rise in Garten's intraventricular curves, which come about 0.01-0.02 second after the *R* peak, are an indication that fairly large portions of the heart musculature are in contraction just before the *S* peak is reached. If we bear in mind that even with the most delicate apparatus the mechanical activity of heart muscle lags 0.004 second behind the electrical activity, we can come to no other conclusion than that the catacrotic limb of the *R* represents very closely the moment when the electrical activity of a large part of the ventricular musculature begins. As our analysis shows that this catacrotic limb of the *R* indicates the development of electric negative potential toward the apex, it is very probable that the down stroke of the *R* to the *S* peak represents electrical activity beginning in the ordinary muscle fibers of the apex of the heart and spreading toward the base.

Before proceeding any farther, we wish to emphasize that the *R* peak does not mark the beginning of the spread of the excitation in the ordinary muscle fibers of the apex sharply. The negative process coming down the main branches of the His-Tawara system enters the ventricle at very small areas from which points the spread in the subendocardial layers will proceed in all directions in such a way that the increase in negativity will be very nearly proportional to the squares of the time. The curve of the spread of negativity in the ordinary muscle fibers of the heart will follow the form of the curve for the Purkinje system very closely. The reader who is familiar with the graphs of functions will readily see how the curve representing the spread of apical negativity in the ordinary muscle fibers if it starts at a point a little before the time marked by the *R* peak will only cause a little

flattening of the curve representing the resultant potential in the heart at first, but that as the negative process spreads more rapidly with time at about the moment marked by the *R* peak the resultant curve will begin to take a different direction

We have not as yet taken into consideration the fact that the maximum of negativity at a point is not present instantaneously but needs a short time for full development. This fact would not cause any modification of our views, as the time for full development of electronegativity at a point is very short and would only tend to prolong the electrical curve for a given set of fibers farther into the curve for a succeeding set and into the curves of mechanical activity. Thus the end of the anacrotic limb of the *R* would represent further development of negativity at points of the basal subendocardium which had received their electronegativity a short period before.

There is one more test of the plausibility of our interpretation. Lewis and Rothschild<sup>3</sup> have shown that the velocity of conduction in the Purkinje system is about from 2.5 to 3 meters per second, and about 400 millimeters per second in the ordinary muscle fibers of the heart. Measurements of the distance from the point where the His-Tawara system spreads out into the arborizations of the Purkinje system to the farthest point on the subendocardium of the apical layer give a conducting path of about 3 cm. It would take the electronegative wave about 0.01 second to reach all parts of the apical subendocardial Purkinje system. From the beginning of the ventricle electrocardiogram to the *Q* peak is from 0.01 to 0.015 second, a result which agrees very well with the above measurements. The distance from the base of the papillary muscles to the farthest points in the basal subendocardium in normal hearts is from 6 to 8 cm. This would give a conduction time of about 0.025 or 0.03 second. From the beginning of the ventricle electrocardiogram to the peak of the *R* is about 0.03 second. Another very good agreement of the facts of velocity of conduction and distance of conduction with the interpretation of the *R* which we have given. The thickness of the basal musculature can be taken as 12 mm in the thicker parts. This would require 0.03 second for conduction of the wave from within outward. From the *R* peak to the end of the *S* wave are 0.03 or 0.04 second. Another good agreement of the "interpretation of the *S* wave with the experimental facts. The calculated times of conduction are all slightly shorter than the corresponding time as derived from the *R* peak and the end of the *S* wave. This is probably due to the fact mentioned above that the negativity takes a short time to develop to its maximum at a point.

According to our analysis of this electrocardiogram which has an *S* wave in lead II, and where the vector corresponding to *S*<sub>II</sub> indicates greater negativity at the apex of the heart than at the base, the base must receive the last increment of action negativity. This fact of the negativity appearing last at the base is in good accord with Einthoven's explanation of the *T* wave.

For a short period following the *S* wave there is no resultant potential difference in the heart despite the fact that the whole of the heart is in activity. This we have already explained as due to the fact that the summation of all the potential differences throughout the whole muscle mass when added as vectors must be zero. There is, therefore, no potential difference produced in parts external to the heart. The *T* wave indicates that there is a resultant potential difference present in the heart within a very short interval following the *S* wave. We shall follow the Einthoven<sup>10</sup> view in explaining the *T* wave. The view held by some that the *T* wave is related to the contraction of the muscle and the *QRS* group to the spread of the excitation process is not in accord with the facts for the contraction process begins a few hundredths second before the *T* wave and the ventricle pressure curve shows a relaxation of the contraction just about where the *T* wave starts.

Some have thought that the *T* wave was the expression of a different process, for example, a metabolic process. This again does not agree with the facts, for we would expect the metabolic process associated with the heart's contraction to precede the contraction or to follow it. The *T* wave begins after the contraction process and ends just a moment after the second sound.

In our opinion Einthoven's explanation is the only logical one. According to Einthoven, the negative process after reaching its maximum about the end of the *QRS* group begins to die out. It dies out more slowly in certain parts than in others, and thus leaves a residual preponderance of negativity at the parts where it begins to decrease last. The decrease in negativity will be a much slower process than the increase. All curves of muscle activity, whether of the action current or the contraction process, show a sharp rise, a short period of maximum and a slow decline of the curve to the initial position.

If we think of our orthodiagram of the ventricle as divided by a horizontal line *PR* running through the center of gravity (Fig. 6) and the arrow as representing the resultant potential differences in the two parts, these arrows have opposite directions and equal lengths during the period following the *QRS* group and before the beginning of the *T* wave, for the resultant electromotive force in the whole heart is zero.

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<sup>10</sup> Einthoven Arch f d ges Physiol **122** 517, 1908

at this time. If we assume the negativity now begins to die out in the lower portion of the heart projection, we may draw the curve *ABC* shown in Figure 7 to represent the dying out of negativity in the apical portion. About 0.02 second later the negativity begins to decrease in the basal portion according to the curve *HDE*. The difference in the ordinates of these two curves is the curve *FTG*<sup>11</sup>. The curve *FTG* approximates very closely the *T* wave of the electrocardiogram in lead II of the heart, whose orthodiagram and electrocardiograms have been used for this analysis of the spread of the excitation process in a normal heart. The construction of Figure 6 was determined as follows. The

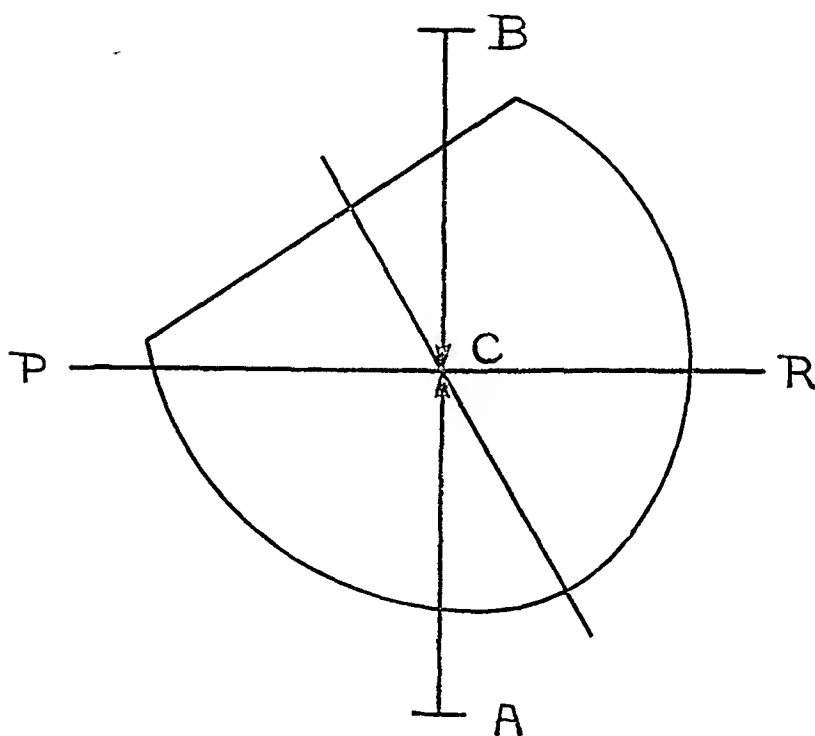


Figure 6

direction of potential difference in the heart was found for a number of points on the *T* wave in lead I and lead II. The values of an angle  $\alpha$  for various points lay between 82 and 93 degrees. The angle  $\alpha$  for various points along the *T* wave is not constant, but if we select an angle  $\alpha$  equal to 86 degrees it will represent the direction of potential in the heart during the period of time in which the *T* wave is recorded with sufficient accuracy for every practical purpose. The angle made by the arrow *BC*, shown in Figure 6, with the line *PR* is an angle  $\alpha$  equal to  $-86$  degrees and the angle  $\alpha$  made by the arrow *AC* with the line *PR* equals 86 degrees.

11 In order to make the curve *FTG* large enough for publication we have multiplied the differences between the ordinates of *ABC* and *HDE* by 4.

In constructing Figure 7 it was necessary to find two curves *ABC* and *HDE*, which would represent the disappearance of negativity in the two portions of heart muscle in such a way that when the one curve, *HDE*, begins about 0.02 second after the other curve, *ABC*, the difference in their ordinates makes a curve closely approximating our *T* wave. In the drawing the distance between the ordinates equals 0.020 second, and between the abscissae 1 millivolt. The ordinates of the curve *FTG* are 1 millivolt equal to the distance between 4 abscissae. This change in scale was only necessary in order that the *T* wave reproduce large enough. We wish to emphasize that our construction is purely hypothetical and based on Einthoven's explanation of the *T* wave. This explanation is the only one which is in accord

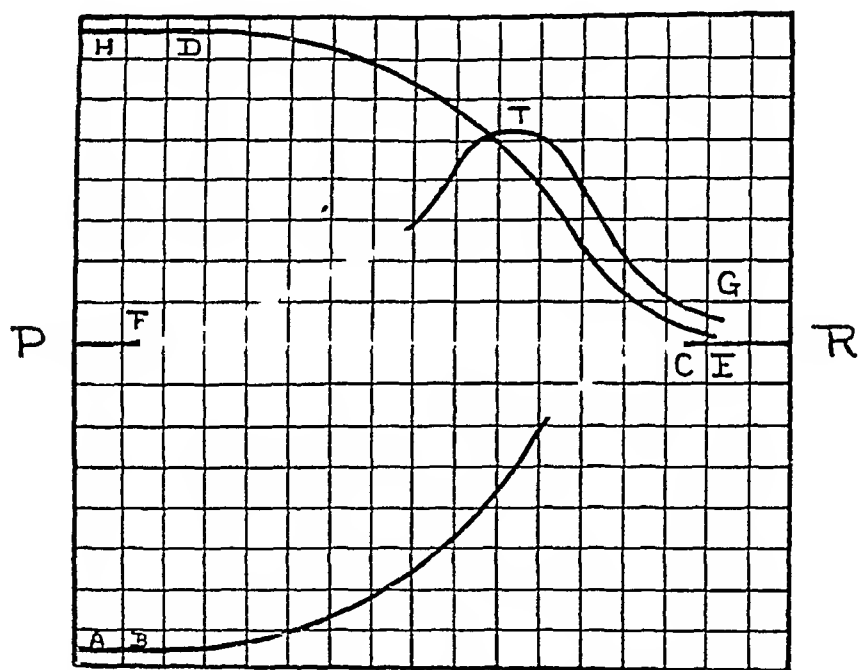


Fig 7—*ABC* is the curve of disappearance of negativity in caudal portion of heart represented in Figure 6. *HDE* is the curve of disappearance of negativity in the portion of the heart above line *PR* of Figure 6. *FTG* is resultant potential difference in heart found by adding ordinates of *ABC* and *HDE*, and multiplying by four in order to make *FTG* large enough to show well in the reproduction.

with all the known facts of physiology, and for the present should be used as a working hypothesis. Mines<sup>12</sup> has shown that by heating the apex of the tortoise ventricle he could shorten the period of apex negativity. In the tortoise heart the *T* wave was negative before heating, and after heating it became upright and had the form of the *T* wave of the human electrocardiogram. Thus by prolonging the base negativity we got the type of *T* wave shown in the normal human



electrocardiogram This seems to be very good experimental evidence for the correctness of the explanation represented in Figure 7 If it were possible to cool the apical portion of the heart represented in Figure 6, thus prolonging the negativity in this portion and in consequence both shifting the curve *ABC* in figure 8 to the right and reducing its slope, we would get a negative *T* wave in the resulting electrocardiogram

The electrocardiograms of five normal hearts have been analyzed by the above method and the same type of propagation of the electro-negative process has been determined for all It so happened that all of the synchronous records taken by us showed *Q* waves in leads II and III, and *S* waves in leads I and II A *Q* wave in lead I would be associated with a shorter path to the left ventricle than the right ventricle, or a position of the right papillary to the left of the center of mass We are not in possession of an electrocardiogram showing this type of propagation in a normal heart, but we have seen them in the collections of other electrocardiographers Some electrocardiograms from normal hearts apparently show no *S* waves in leads I and II We need not infer a fundamentally different type of propagation for these cases Either the vector representing apical preponderance of negativity lies in or nearly in a sagittal plane and therefore has little influence on our frontal leads or the spread of negativity from the apical Purkinje system into the ordinary muscle fibers is so little ahead of the spread into the basal muscle fibers that the net result is simply a rapid descent of the *R* wave with a gradual decline in its gradient toward the end In other words, the apical muscle fibers receive their negativity first, causing a neutralization of the basal negativity due to the excitation in the basal Purkinje system, but the ordinary basal muscle fibers receive their negativity also a very short time after the apical, and in this case the lag of negativity at the base is so small that the sharp descent of the *R* is soon changed into a less steep gradient and does not end with an *S* wave

Some electrocardiograms do not show a *Q* wave in leads II or III In these cases we infer that the papillary muscles lie high up on the ventricle walls so that the spread of negativity toward the base is more rapid than toward the apex

Figure 8 is the orthodiagram of a heart showing left ventricular dilatation and hypertrophy in a patient suffering from myocardial degeneration The electrocardiogram was the typical electrocardiogram of so-called left ventricular preponderance, high *R*<sub>I</sub> and deep *S*<sub>III</sub> The term "left ventricular preponderance" does not apply to the electrocardiogram as the arrows in Figure 8 show, for they indicate that the characteristic form of this electrocardiogram is determined

by a preponderance of electronegativity in the right side of the heart. This is to be explained as follows. The dilatation and hypertrophy of the left ventricle cause an increase in the normal length of the His-Tawara bundle branches in the left ventricle. The increase in length of conducting path is accompanied by increase in time of conduction to the left ventricle. The right ventricle, therefore, gets its negativity 0.01 or 0.02 second earlier than the left ventricle and this determines the direction of the vector. As the left ventricle increases in negativity it merely compensates the right ventricular preponderance until the moment when the whole of the right and left ventricles are negative and the resultant vector is zero.

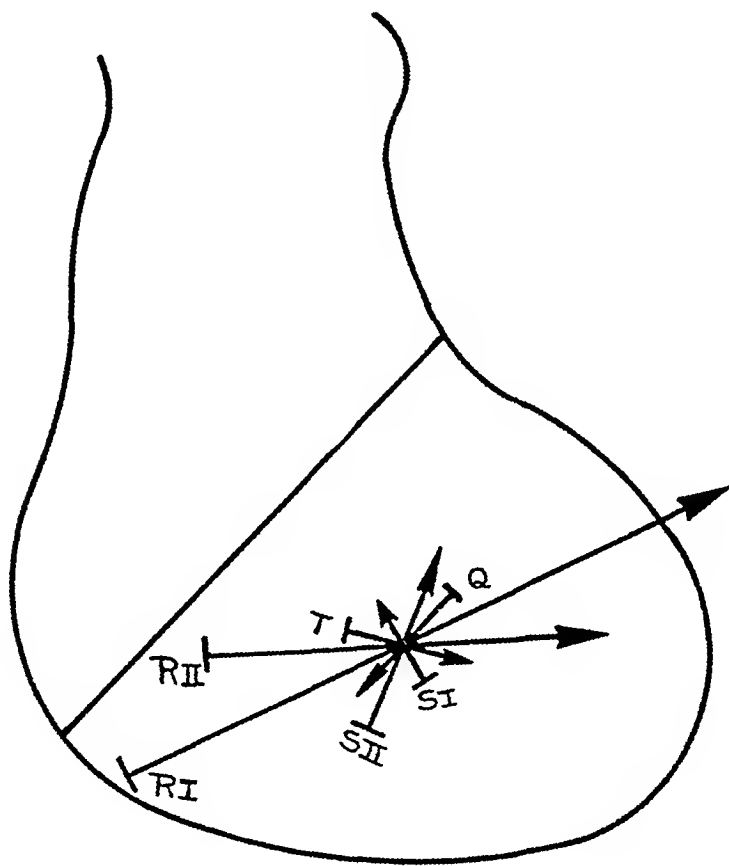


Fig 8—Orthodiagram of heart with predominating left ventricular enlargement with vectors of potential corresponding to various points on electrocardiogram

In Figure 8 it will be seen that *Q* indicates negativity of the left side of the heart. We are at present unable to explain this, excepting on the assumption that in this case the dilatation and hypertrophy took place in such a way that the right papillary muscle came to have a position to the left of the center of gravity. If we recall the topography of the heart we see that the septum does not run in a sagittal plane, but in a plane lying between the sagittal and frontal planes.

In other words, the right ventricle overlaps the left to a certain extent in a frontal projection. This overlapping must be increased in certain types of dilatation of the ventricle through the increase in size of that portion of the left ventricle lying behind the right ventricle in frontal projection. The right papillary muscle comes off the septum near its anterior border. It could very well be, that in certain forms of dilatation of the left ventricle, the right papillary muscle comes to lie to the left center of gravity of the heart muscle mass. From this point the negative process spreads throughout the right ventricle a little ahead of the spread in the left. We would then get vectors corresponding to those in Figure 8, which is not a pure left ventricular dilatation. The patient was decompensated and showed signs of beginning relative mitral incompetence.

We have analyzed about twenty electrocardiograms of patients with systolic blood pressures ranging from 250 to 320 mm of mercury. At the time the records were made none of them showed signs of mitral incompetence, and the roentgen rays indicated that the increase in size of the heart was due very largely to dilatation and hypertrophy of the left ventricle. The electrocardiograms of all showed a high  $R_I$  and deep  $S_{III}$  and the construction of the direction of potential difference in the heart showed that the form of the electrocardiograms was due to a preponderance of electronegativity in the right ventricle throughout the period of the  $QRS$  group due to increase in length of the path of conduction on the left side. Most of these cases showed no  $Q$  as in Figure 8, the arrows pointing toward the left from the moment that the excitation process got into the ventricles.

To my mind there is no question that the form of the electrocardiogram in pure left ventricular dilatation and hypertrophy always shows a high  $R_I$  and deep  $S_{III}$ , and an analysis shows that in these cases the form is due to preponderance of right ventricular negativity. In Figure 8 the potential difference  $R_{II}$  was present in the heart about 0.01 second after  $Q$ .  $R_{II}$  was followed by  $R_I$  in about 0.01 second.  $S_{II}$  followed in another 0.02 second and  $S_I$  in another 0.01 second. The duration of the  $QRS$  group from the beginning of the ventricle electrocardiogram to the point where the catacrotic limb of the  $S$  ended was 0.08 second. In most of the electrocardiograms of pure left ventricular enlargement of our collection the duration of the spread of negativity in the ventricles is longer than this, from 0.10 to 0.12 second. This increase in length of time of the propagation of the excitation process in these hearts must be ascribed to the lengthening of the path in the left ventricle and in the increased thickness of the walls. Most of the electrocardiograms of predominating left ventricular enlargement in our collection have negative  $T$  waves in lead I.

and positive *T* waves in lead III. This indicates that the negative process lasts longest at the left base, and we can infer from this that the left base received its negativity last. Of course we can not infer too much from the *T* wave in these hearts, for the musculature is no longer normal in them.

Just as our construction of the direction of the potential difference in the heart has shown that it is the preponderance of right ventricular negativity that determines the form of the electrocardiogram in pure left ventricular enlargement due to an increased length of the path of conduction in the left ventricle, so also our analysis of electrocardiograms from bundle branch lesions has shown us that the prevalent

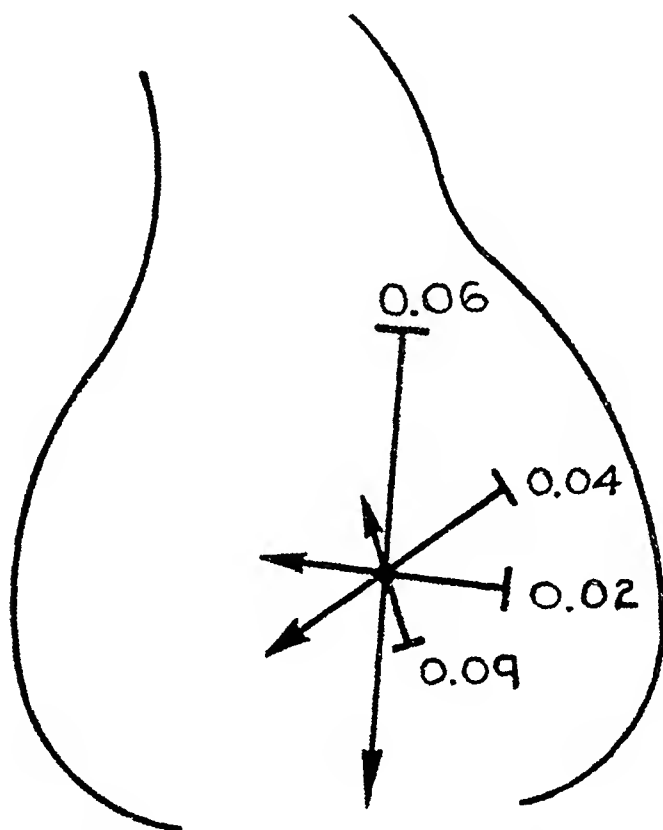


Fig 9—Orthodiagram of heart with mitral stenosis and tricuspid insufficiency with vectors of potential corresponding to various points on electrocardiogram. Time in seconds after onset of ventricular electrocardiogram.

conceptions here also are wrong. A high *R*<sub>I</sub> and deep *S*<sub>III</sub> means left bundle branch block, for the vectors show that the right heart is negative first and that as the left heart becomes negative the right sided preponderance is neutralized and the resultant approaches zero. Vice versa, a high *R*<sub>III</sub> and deep *S*<sub>I</sub> in bundle branch block indicates right bundle branch lesion for the construction of the direction of the potential difference in the heart shows that the left side is negative first and the vector is swung toward the right about 0.05 or 0.06 second after the beginning of the electrocardiogram.

In a purely right ventricular dilatation and hypertrophy the electrocardiogram shows a deep *Si* and high *RIII*. In case there is both left and right sided enlargement the same is true, provided that the right sided enlargement is greater than the left sided enlargement. Construction of the direction of potential in the ventricles shows that in these cases the left side of the heart is negative first and that the right ventricle receives its negativity later because the increase in size of the right ventricle necessitates a greater length in the right bundle branch and in the path of the spread in the subendocardial system of Purkinje fibers. Figure 9 is the orthodiagram from a case of mitral stenosis with relative tricuspid insufficiency. Into the roentgenogram of the heart the arrows have been drawn as usual. In this drawing the negative ends of the arrows are not marked as *Q*, *R* and *S*, but the time after the beginning of the ventricle electrocardiogram has been used to designate the arrows. The negativity begins in the left ventricle toward the apex and then spreads to the left base. The velocity of the propagation is very slow, probably both because of the increased length of path and because the heart muscle has been damaged. Necropsy measurements of the length of the right bundle branch down to near the papillary muscle showed it to be about 2 cm longer than either of the left bundle branches. In other words, the left heart receives its excitation wave about 0.01 second before the right ventricle. The average of measurements from the neighborhood of the papillary muscles to the base of the heart showed that the path in the dilated right ventricle was about  $3\frac{1}{2}$  cm longer than in the left. These measurements show that the left side of the heart must get its negativity first, and that in so-called "right ventricular preponderance" we really have a left ventricular preponderance of action negativity shown in the electrocardiogram.

#### CONCLUSIONS

1 The method of the equilateral triangle is sufficiently accurate for determining the frontal plane projection of the direction of the potential difference in the human ventricle and its "manifest" or maximum derived value.

2 It is possible to follow the spread of the excitation process throughout the ventricles by following the change of direction of the vector of potential difference throughout a heart cycle and by making use of our knowledge of the architecture of the His-Tawara-Purkinje system, of the approximate rates of conduction of the negative process in this system and in the ordinary muscle fibers and of the time of onset of the first heart sounds and ventricle pressure curve.

3 The excitation process beginning first in the subendocardial layers of the Purkinje system in the neighborhood of the papillary muscles, usually a little earlier in the right ventricle spreads first to the apical layers causing the *Q* wave. The excitation process is quickly conducted to the basal arborizations of the Purkinje system giving rise to the anacrotic limb of the *R*. While the excitation process is being propagated through the basal Purkinje system the process in the apical area of the Purkinje system is spreading to the ordinary muscle fibers of the apex. By the time the peak of the *R* is reached the negativity in the ordinary muscle fibers of the apex is of sufficient magnitude to neutralize the preponderance in the basal Purkinje arborizations and cause the catacrotic limb of the *R* and the *S* peak. The process meanwhile is passing from the basal Purkinje system into the ordinary muscle fibers of the base. Their negativity increases until the effect of the apical fibers is counteracted and the *S* wave is reduced.

4 The negative process begins to die out at the apex first leaving a preponderance of negativity at the base. This gives rise to the *T* wave.

5 The form of the electrocardiogram in hearts which have left sided enlargement is due to the increased length of conducting path in the left ventricle. The right ventricle receives its negativity first.

6 In right sided enlargement the left ventricle receives its negativity first because the path of conduction to the right ventricle is longer. The form of the electrocardiogram in these cases is due to a preponderance of negativity on the left side.

7 The diagnosis of right and left bundle branch lesion as commonly made is probably wrong. In left bundle branch lesion we should find a high *R* in lead I and deep *S* in lead III. In right bundle branch lesion we get a deep *S* in lead I and high *R* in lead III.

# A CLINICAL STUDY OF YELLOW FEVER <sup>1</sup>

OBSERVATIONS MADE IN GUAYAQUIL, ECUADOR IN 1918

CHARLES A ELLIOTT, M D

CHICAGO

The following report is based on the study of about seventy cases of undoubted yellow fever admitted to the lazaretto<sup>1</sup> of Guayaquil, Ecuador, from July to September, 1918. Fifty consecutive cases, including all grades of severity, admitted during the latter part of the investigation, were studied carefully according to a definite plan.

The cases observed by no means represent all the cases that occurred in Guayaquil during the period of study, for not all yellow fever patients were concentrated in the lazaretto by the authorities.

An attempt was made to obtain early cases. One patient was admitted during the first day of his illness, ten hours after an abrupt onset, eleven patients were admitted on the second day, and thirteen on the third day. The others were admitted on various days and as late as the ninth day. Nine cases were considered light and forty-one as severe cases. Eleven patients were admitted in extremis, delirious or comatose.

## EPIDEMIOLOGY

Guayaquil is an endemic center of yellow fever. While no information is available as to the total number of yellow fever cases in the city during the period of this study, there undoubtedly were many cases of all grades of severity. During 1917, 226 patients were admitted to the lazaretto. Of these, sixty-seven died.

The patients in this series were, for the most part, from the poorer classes. Five were soldiers recently recruited from the interior, eleven were servants. There were nine children. The others were

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\* Read before the American Society of Tropical Medicine, Atlantic City, N. J., June 17, 1919.

<sup>1</sup> This clinical study of yellow fever is part of an unpublished report submitted to the International Health Board of the Rockefeller Foundation which appointed the following commission for the study of yellow fever during the summer of 1918: Dr. Arthur I. Kendall, chairman, Dr. Hideyo Noguchi, bacteriologist, Dr. Mario G. Labrado, sanitarian, Mr. Herman E. Radenbaugh, chemist, and Dr. Charles A. Elliott, clinician.

<sup>1</sup> The yellow fever hospital is conducted as a part of the sanitary service of the municipality. I wish to express my thanks to Dr. Leon Becerra, director of the sanitary service of Ecuador, to Dr. Wenceslao Paraja, chief of the medical service, and to Dr. Jorge Larrea, director of the laboratories, for daily consultation and advice.

housewives, small shopkeepers, laborers, policemen etc. A husband and wife, and a brother and sister are included. Of forty-nine patients only two were natives of Guayaquil, nine had lived in Guayaquil for less than two months, the others came principally from the mountain provinces in the interior, eleven from Ambato, seven from Quito, six from Cuenca, four from Latacunga and three from Riobamba.

The houses from which the patients came were found to be quite evenly distributed throughout the city (Fig 1). In four instances two or more patients came from the same house, a military hospital,



Fig 1—Spot map of Guayaquil showing distribution of forty-seven of fifty consecutive cases admitted to the lazaretto.

a military barracks and two private homes. The homes of the patients were made of cane wood or corrugated iron, usually two stories high, the ground floor was constructed of mud or wood. About an equal number of patients lived on the ground floor and on the second floor. The type of house seemed to have little influence on the incidence of infection. *None of the houses were screened.* Inquiry showed that mosquitoes, often in great numbers, were present in all of the houses. The common house mosquito *Aedes calopus* Meigs (*Stegomyia calo-*



pus), was found breeding in these homes. Bedbugs were common and head lice were found on most of the women and children admitted to the hospital. Thirteen of thirty-one patients habitually went barefooted, and many were admitted with numerous sores on the legs from infected mosquito bites.

While the mosquito, *Aedes calopus*, Meigs, has been considered the chief, if not the only, means of transmission of yellow fever, other means, such as direct transdermic infection, seem possible in view of the apparent similarity of yellow fever and infectious jaundice. That there were many habitually barefooted patients with infected sores and that yellow fever was experimentally produced in animals by Noguchi by inoculations through the unbroken skin, would seem to support this view.

It seems fitting to call attention to the discovery by Noguchi<sup>2</sup> of a minute organism in the blood and tissues of these patients. He has provisionally called the organism the *leptospira icterioides*. He was able to transmit the organism to experimental animals by the injection of blood and of tissue emulsions from yellow fever cases, producing in guinea-pigs clinical and pathologic manifestations similar to those found in the human cases. By special methods these organisms were obtained in pure culture. They resemble the causative agent of infectious jaundice morphologically, but are distinct immunologically. Injections of pure cultures into guinea-pigs produced symptoms and lesions closely paralleling those of human yellow fever. From the blood, liver and kidneys of guinea-pigs inoculated with blood from yellow fever patients, organisms identical with those isolated from human blood were found. The disease was readily transmitted from animal to animal.

#### GENERAL CLINICAL DESCRIPTION

The clinical picture of yellow fever as seen in these cases was most striking. Noteworthy were the rapid onset and progress of the disease, the usually low and short fever course accompanied by bradycardia, congestion of the face, sclerae and gums, the subsequent afebrile period of apparent intoxication with increasing jaundice, hemorrhage and nephritis. Prompt death or rapid and complete convalescence resulted. The whole course of the disease was short. The patients who had light infections recovered, on an average, by the end of the first week, the patients who had severe infections recovered by the end of three weeks. In fatal cases death occurred as early as the fourth and as late as the eighteenth day, on the average on the eighth day.

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<sup>2</sup> Noguchi, H. Etiology of Yellow Fever. I. Exper. M. **29** 547, 1919, **30** 1, 87 401, 1919.

Fever was present for the first few days only as a rule dropping to normal on the fifth sixth or seventh day. The patients with light infections then recovered rapidly, while those with severe infections were desperately ill during the afebrile period of intoxication.

It seems proper to speak of two periods first the period of *incubation* of four or five days' duration with fever, congestion headache, backache epigastric and general abdominal pain and tenderness muscle tenderness, nausea and vomiting. During this period the patient is feverish, the face and conjunctivae are suffused, the gums are swollen. The patient is restless and apprehensive. The urine shows increasing evidence of nephritis with progressively increasing albuminuria and cylindruria. The general congestion gradually gives way to the second period, apparently one of *degeneration* during which the patient is extremely toxic, relaxed and weak. Jaundice increases to an extreme degree, and nausea with vomiting often "black vomit" occurs. Hemorrhages occur from any source gums, gastro-intestinal tract, nose, urinary tract or uterus and into the skin or conjunctivae. These hemorrhages may be slight and intermittent, as, in the skin, from petechiae to areas several centimeters in diameter, or occasionally, as epistaxis or nosebleed. The hemorrhages may be continuous and alarming as from the gum edges, nose, or as repeated "black vomit" and melena. There may be free bleeding from an abraded skin surface, from the uterus, or from the urinary tract.

There is much general abdominal tenderness, especially in the epigastrium. The liver edge is exquisitely tender. The patient complains of headache, backache and general aching of the extremities. The stomach is intolerant of food. Persistent vomiting often occurs. Uremic symptoms frequently develop. Diminution of urine or complete anuria occurs also restlessness headache, hiccup, delirium, stupor, coma and convulsions. Albuminuria increases to an alarming extent. From a trace of albumin on the second day there may be an increase to 4 or 5 gm per liter on the seventh day coincident with intense cylindruria mostly of granular, blood or epithelial casts, paralleling the albumin. Fotor ex ore may become intense and characteristically the odor of the deadhouse. The pulse is full soft slow, frequently dicrotic becoming fast in extremis.

The patient may die during the second week apparently uremic, or convalescence may ensue rapidly while the jaundice increases. In the latter event hemorrhages cease the gingivitis subsides. All mucous membranes appear jaundiced and anemic the abdomen is retracted and less tender. The patient appears dried out emaciated hungry. Albumin and casts disappear rapidly from the urine. The patient asserts that he is well after two or three days and wishes to be up and

about Strength and body weight are rapidly regained Convalescence is rapid and apparently complete in a very few days

#### CLINICAL FINDINGS IN DETAIL

*Anamnesis*—The symptoms were fairly uniform In uncomplicated cases, a precipitous onset was the rule A feeling of uneasiness, particularly in the epigastrium, and aching of the head, back and extremities were first noticed Fever developed rapidly, often preceded by a chill or chilliness Nausea and vomiting frequently occurred from the start, the vomit being usually "bilious," although "black vomit" was sometimes present as early as the second day Fever, headache, backache, general muscular and epigastric tenderness or pain, nausea and vomiting persisted in various combinations until admission to the hospital



Fig 2—Severe case (Case 47) with recovery Girl, 7 years of age, on fourth day of disease Multiple hemorrhagic areas into the skin are shown

Certain patients who had been suffering from malaria for varying periods, gave a history of unusual symptoms, such as the onset of nausea, vomiting, epigastric tenderness, head and backache, and persistent fever In such cases the diagnosis was uncertain until typical manifestations of yellow fever developed

*Physical Examination*—On admission, the patient appears restless with anxious expression, the face is flushed, the conjunctivae are injected, the gums are swollen and bleed easily on pressure Hemorrhages into the skin are found occasionally (Fig 2), varying from 0.1 cm to several centimeters in diameter They are usually irregular in outline Infected mosquito bites on the forearms or legs are seen frequently The mucous membrane of the mouth is congested Herpes labialis was present only in two cases The lymphnodes are not

enlarged The lungs, except in terminal hypostasis or pulmonary edema, are clear The heart is usually normal Occasionally, during the height of the disease, a precordial systolic murmur was heard, and rarely premature contractions were noted The abdomen is, usually diffusely tender, the epigastrium and liver edge are exquisitely tender The liver was not definitely enlarged, except in a few cases The spleen is not palpable in most cases of frank yellow fever, it was definitely enlarged only in suspected malarial cases Tenderness on pressure over the kidney region in the flanks is usually marked The skeletal muscles are ordinarily tender during the entire course of the disease

During the second period of the disease the patients are usually quiet, relaxed, jaundiced, weak, apparently dried out and very ill

There is a loss of body weight, averaging about one pound per day during the active course of the disease The most marked loss of weight recorded was  $17\frac{3}{4}$  pounds in sixteen days With the onset of convalescence the normal weight is regained promptly

*Temperature*—The fever is relatively low, continuous and usually of short duration After reaching its height on the first day, the temperature remains remarkably constant for three or four days and then gradually drops to normal from the fifth to eighth day In a few cases observed early a slight remission on the second or third day was noted The fever usually lasts about a week In four patients it was normal on the fourth day In three apparently uncomplicated cases it remained elevated until the eleventh day When the patient's condition appears gravest the temperature is usually normal or slightly subnormal

*Pulse*—The pulse rate is usually relatively slow during the febrile period, in proportion to the fever curve Early and during the post-febrile period the pulse rate is proportional to the temperature curve The bradycardia is moderate and relative, rarely absolute A pulse rate of 50 or less was observed fourteen times and constituted a grave sign Eight of these fourteen patients died, the others recovered after very severe courses A terminal rise in the pulse rate is the rule The pulse is usually full, soft and regular, occasionally dicrotic and rarely intermittent

*Respiration*—In the first few days of the disease there is a subjective dyspnea of which the only objective evidence is an occasional deep sighing respiration together with a peculiar whistling expiratory note Except for this dyspnea, the respiration in the light and moderately severe cases was apparently normal through the entire course of the disease In the severe cases, those that were evidently uremic, a variety of respiratory abnormalities were encountered Deep expirations, accompanied by moaning and groaning, were common, air hunger

of maximum intensity, lasting irregularly for hours, or Cheyne-Stokes respiration, typical or variously modified, were common as terminal events

*Jaundice* —Jaundice is a constant though variable manifestation in all cases. It is usually proportional to the severity of the disease, inconspicuous in most of the light cases, although sometimes marked as compared to other manifestations, and intense in the severe cases. It appears, as a rule, on the third or fourth day, occasionally as early as the second day. A maximum intensity is reached about the tenth day and continues well into convalescence. Jaundice was still intense in some cases at the time of discharge when the patient was otherwise apparently well. In three light cases it appeared for the first time during convalescence, on the eighth, tenth and fifteenth day, respectively. Fifteen patients were admitted before jaundice had appeared. All patients admitted in extremis were intensely icteric.

The pigmentation is first noted in the congested conjunctivae, increasing as the congestion disappears. The skin and mucous surfaces are discolored later. Skin jaundice was sometimes difficult to detect because of the dark complexions of the patients. The blood serum and the urine are often markedly pigmented, out of proportion to the degree of jaundice evident elsewhere, and remain so for a longer time.

The jaundice itself is apparently nontoxic, skin itching does not occur. On only two occasions were patients observed scratching the skin, although attendants were constantly watching for this manifestation. At the end of convalescence intensely jaundiced patients appear to be free from obvious toxic symptoms.

The jaundice is apparently primarily of the dissociated type. The blood serum of all patients definitely pigmented gives a positive, often intense, Gmelin test for bile pigment, only four of ten serums tested gave a weakly positive Pettenkofer test for bile salts on aqueous dialysates.

The urine, always intensely pigmented, uniformly gives an intense Gmelin test for bile pigment but a negative or, at most, a faintly positive, Hay or Pettenkofer test for bile salts. In all markedly jaundiced patients the foam of the urine is definitely yellow. Some specimens showed evidence of large amounts of urobilin, although some of the most intensely pigmented urines showed none.

The stools, in a few cases, were distinctly clay colored, but in most cases they were dark brown and contained much blood.

From the clinical and postmortem evidence one must conclude that the degenerated liver of yellow fever is incapable of performing its function, that it not only acts as a barrier to the normal turnover of

pigment in the body, but that it is also incapable of secreting bile salts. The jaundice is, therefore, primarily a hepatic dissociated jaundice, although it is evident from the presence of traces of bile salts in the blood in three of eight cases tested, that there is also some resorption as a result of bile capillary obstruction.

*Blood*—Blood examination shows little that is characteristic. The red blood cell count is rather high in proportion to the low percentage of hemoglobin, possibly due to the fact that most of the patients had recently left the mountains to reside at the sea level. The average count was within the normal range, although three counts of more than six million and nine of less than four million were obtained. The lowest counts were obtained in patients having uncinariasis.

The average white blood cell count\* is about normal. A definite leukopenia of less than 4,000 occurred in only nine cases. High counts, from 13,000 to 49,000, were obtained in moribund patients, usually uremic, although it is noteworthy that some comatose patients showed normal white counts. Apparently, there is no rule that can be applied to the light and severe cases in so far as the white blood count is concerned, as both high and low counts were obtained in both groups.

The hemoglobin, as estimated by a Dare instrument, is uniformly low. Estimations between 40 and 60 per cent were common, more than 90 per cent was found in three cases, estimations of from 80 to 90 per cent were obtained in ten cases. One patient with uncinariasis had 28 per cent hemoglobin. Hemoglobin does not drop proportionally as jaundice progresses. The estimation of the percentage of hemoglobin is, to some extent, rendered inaccurate because of the presence of bile pigment in the intensely yellow blood serum of all severe cases. Higher readings than the actual amount of hemoglobin present would warrant are accordingly obtained. A drop in hemoglobin was noted in a few severe cases as the disease progressed, from 65 to 58 per cent and from 48 to 28 per cent. On the other hand, the percentage of hemoglobin seemed to increase as the disease progressed in some cases, due, possibly, to the large amount of bile pigment present in the blood plasma early and to dehydration later in the course.

The differential count shows only normal variations. An unexplained eosinophilia of 30 per cent developed in one case, while under observation. A vacuolar degeneration of the white blood cells was present in thirteen of eighteen blood smears, especially examined for this point and seemed most marked in moribund patients. Blood platelets are always present, apparently in more than the normal number.

The coagulation time of the blood is well within the normal range, averaging from one to three minutes even in patients with continuous

hemorrhage In only three cases was the coagulation time found to be more than four minutes

Aestivo-autumnal malarial parasites were found in the blood of five patients, while in a few cases with undoubted coincident malaria they could not be detected

The washed red blood cells show normal resistance to hypotonic salt solution Fifteen tests on eight jaundiced patients gave results which were well within the normal range, although there seemed to be a range of hemolysis slightly wider than the normal, for example, hemolysis beginning at 0.40 per cent sodium chlorid solution and complete at 0.28 per cent in one case, and a range of 0.42 per cent to 0.30 per cent in another case No satisfactory explanation of this is evident

*Blood Pressure*—The blood pressure is uniformly low, systolic 110 or less and diastolic 65 or less, as a rule Otherwise nothing distinctive was observed The pulse pressure is not distinctive

*Hemorrhage*—Hemorrhage is one of the distinctive manifestations of the yellow fever cases of this series It was observed clinically in all severe cases which remained under observation long enough for this point to be determined Thus, hemorrhage, in one form or another, was observed in thirty-four cases, it was absent in seven cases, only one of which was considered severe Eight patients were not under observation long enough for the determination of this point Hemorrhage occurs in many forms, and apparently, from almost any tissue The nasal and gingival mucous membranes and the gastro-intestinal and genito-urinary tracts are the principal sites of hemorrhage In all of the nine necropsies performed extensive hemorrhages were found, principally into the gastro-intestinal tract, lungs, kidneys, papillary heart muscle, uterus, mesenteric glands, suprarenals and on the subserous surfaces of organs such as the heart, lung, stomach, bowel, liver, gallbladder and kidneys

Alarming hemorrhages occurred from the gums (Figs 3 and 4), gastro-intestinal tract, uterus, or urinary tract in sixteen cases, lasting often for days, as in the case of bleeding from the gums, stomach or bowel, or appearing suddenly and intermittently as from the nose or uterus

Slight epistaxis occurred early in only seven cases, and this fact was elicited only on inquiry Severe epistaxis occurred later in twelve cases from the fifth to the twelfth day Bleeding from the gums was noted in twenty-one cases Blood can be expressed from the gums of most patients at the height of the disease In nine cases the hemorrhage was alarming, continuing for days "Black vomit" occurred while under observation in fourteen cases, it was absent in seventeen

of thirty cases observed long enough to determine this point. It had occurred in all of the cases in which a postmortem examination was made. The vomitus is for the most part of coffee-ground appearance, in two cases bright red blood was present.

Hemorrhage into the skin, with areas from one millimeter to several centimeters in diameter, was observed in seven cases. Free bleeding from the surface of the thighs following irritation as a result of prolonged menstrual flow, was alarming and constant in one patient. Uterine hemorrhage occurred in three cases, it was spontaneous and alarming in two cases. Hematuria continuing for days was observed in two patients.

In general, hemorrhage occurs in all severe cases of yellow fever during the second and third weeks. The light cases do not bleed. The administration of horse serum in six cases had no perceptible effect on the bleeding.



Figure 3

Fig 3—Boy, 11 years of age (Case 32), sixth day of disease. Gums swollen and bleeding, sclerae congested, intense jaundice, recovery.



Figure 4

Fig 4—Severe, fatal case (Case 1), male, 23 years of age, fifth day of disease, twenty-four hours before death. Herpes labialis, swollen and bleeding gums and intense jaundice.

It is significant that the hemorrhage does not parallel the jaundice. Hemorrhage is greatest at the height of the disease, while jaundice reaches its maximum after convalescence has begun and persists to a marked degree well into convalescence.

The facts that the coagulability of the blood is normal, that the administration of horse serum is without effect and that the hemorrhage does not parallel the jaundice, seems to indicate that hemorrhage in these cases is due to injury to the vessel walls rather than to some abnormal condition of the blood itself, such as a deficiency of calcium or the presence of bile salts and pigments. These facts seem to indicate that there is a degeneration of blood vessel endothelium proportional to the degree of general parenchymatous degeneration.



*Urine*—The urine in all cases is very highly colored, from dark yellow to olive green, with yellow foam. The amount passed in one day varied from an average of 700 cc to complete anuria, which usually foreshadowed death. Except in moribund cases, the amount of urine is directly proportional to the fluid intake, and can always be increased by increasing the intake even in the presence of persistent vomiting. The intestinal tract is apparently able to absorb fluid, and the kidneys are apparently able to excrete it in spite of intense degeneration.

Albumin appears as a trace on the second or third day, increases rapidly to enormous amounts, 3 or 4 gm per liter, during the second week, and then decreases gradually and finally disappears entirely during the third or fourth week. The albuminuria reaches its height several days after the termination of fever. During the second and third days casts appear in great quantities, paralleling the albumin. These casts are chiefly of the large granular type. They are thickly matted together in the centrifuged specimen.

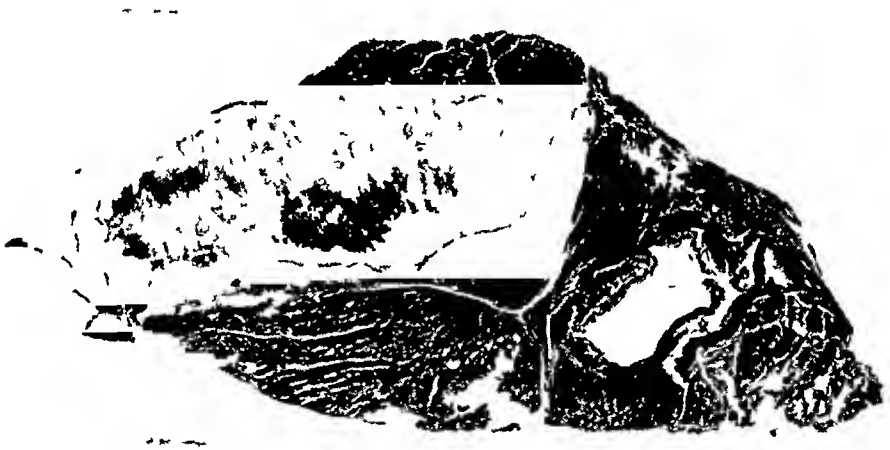


Fig 5—Heart, showing superficial, punctate hemorrhages scattered over the surface.

In light cases albumin and casts are constantly present out of proportion to the other manifestations of the disease, a phenomenon which is of value in diagnosis. Red blood cells are present in all urines at the height of the disease. Swollen, round, apparently detached endothelial cells with large nuclei are numerous, apparently paralleling the other manifestations of nephritis, although they often appear earlier and persist later than the intense cylindruria. Bilirubin was always present (Gmelin test), urobilin was frequently demonstrable by Schlessinger's test but appears least intense in the most highly pigmented urines, bile salts were often demonstrated by Hay's and

Pettenkofer's tests, though the reactions were not as marked as were those for bile pigments. In general, the urine gives evidence of an intense nephritis which persists after the fall of temperature and well into convalescence. The disappearance of all signs of nephritis was observed in all patients who recovered and was remarkable because of the apparent intensity of nephritis attained.

*Uremia*—Uremia is a terminal event in all fatal cases. Of twenty-three patients that showed well marked uremic manifestations, only three recovered, two of the three were wildly delirious on admission. Uremia is usually heralded by a fall in the amount of urine passed in twenty-hours. When complete anuria occurs death usually follows within a few hours. Four patients voided no urine for twenty-hours, two of these recovered.

The following manifestations of uremia were noted: air hunger, a peculiar whistling respiration, precordial distress, headache, backache, persistent vomiting, hiccup and, finally, delirium, Cheyne-Stokes respirations, convulsions and coma.

*Stools*—Most of the patients harbored intestinal parasites. Ova were found in nine of fourteen stools examined. *Uncinaria duodenale* were found in two patients, *ascaris lumbricoides* in six patients and *amebae dysenteriae* in two patients. Lumbricoid worms were frequently present in the vomitus or stools during the height of the disease.

#### COMPLICATIONS AND SEQUELS

Complications and sequels are uncommon. Parotitis occurred in two cases, phlebitis in one case, acute pain and swelling in the joints, interpreted but not demonstrated as hemorrhage, in three cases. A persistent diffuse bronchitis, interpreted as secondary to hemorrhage into the lung, was present in two cases. Secondary infection was suspected in a few cases, but was demonstrated only once during life. In the nine cases in which a postmortem examination was made there were no findings, such as exudates, endocarditis, pneumonia, etc.

#### CONVALESCENCE

Convalescence was rapid in all cases which terminated in recovery, although some patients were weak and many showed varying grades of jaundice at the time of discharge. The latter considered that they were in their usual state of health in spite of the presence of jaundice. No other ill effects of the disease could be detected. Complete restitution from the universally present extreme nephritis apparently occurred in all cases. A few patients were anemic and in poor health as a result of preexisting disease, such as uncinariasis, but as far as the

effects of yellow fever were concerned, complete recovery seemed assured in all of the discharged patients. The rapid and complete recovery of all patients who did not succumb was a constant source of wonder, particularly as contrasted to the incomplete recovery often seen in other familiar severe infectious diseases.

#### DIAGNOSIS

The diagnosis was ordinarily not difficult, even as early as the second or third day, and by the end of the fever course it was established beyond question, even in light cases. The chief diagnostic points are enumerated in the order of their importance.

- 1 The fact that the patient was a foreigner and not a native of Guayaquil or had recently arrived from the interior. The local physicians consider it practically impossible that a child, born in Guayaquil, can grow to maturity without developing yellow fever and, therefore, become immune, or that a susceptible adult can live long in Guayaquil without becoming infected.

- 2 A low continuous fever course with relative bradycardia. A fever of 40 C or more speaks against yellow fever.

- 3 Nausea and vomiting. "Black vomit" is practically diagnostic.

- 4 Epigastric pain and tenderness, often intense from the beginning.

- 5 Rapid and progressive development of nephritis, with albumin present as a trace on the second day and increasing to from 1 to 3 gm per liter on the fourth day.

- 6 Flushed face, injected conjunctivae, swollen and bleeding gums.

- 7 The gradual and progressive development of jaundice, apparent in the conjunctivae as early as the third day.

The greatest difficulty in the diagnosis of yellow fever occurred in cases of malaria in which yellow fever developed subsequently. In these cases the high fever course of malaria gave way to the lower but more continuous fever course of yellow fever, associated with a relative bradycardia not previously present. The lower temperature continued for four or five days. After a few days, during the convalescence from the yellow fever, the high temperature of malaria, not always intermittent, recurred (Case 13). The plasmodium was not always demonstrable in the blood, but these cases readily responded to one or two deep injections of quinin. The differentiation of cases of cerebral malaria was difficult and often impossible, except at necropsy. In children, the manifestations of yellow fever were apparently the same as in adults.

## PROGNOSIS

The degree of severity of a case of yellow fever could not be foretold at the time of admission. Those patients who were admitted early with much facial congestion, conjunctival injection, swelling of the gums and restless and apprehensive facies and dyspnea, had grave infections which usually were fatal. Tachycardia was always considered of serious import. Uremic manifestations, such as air hunger, restlessness, delirium and coma accompanied by a diminished output of urine decreasing to the point of anuria, were grave signs though not necessarily fatal.

The physical condition of the patient at the time of admission did not seem to have much relation to the progress of the disease. Some patients who had previously been in apparent good health died, while others, debilitated from malaria, uncinariasis and amebic dysentery, recovered.

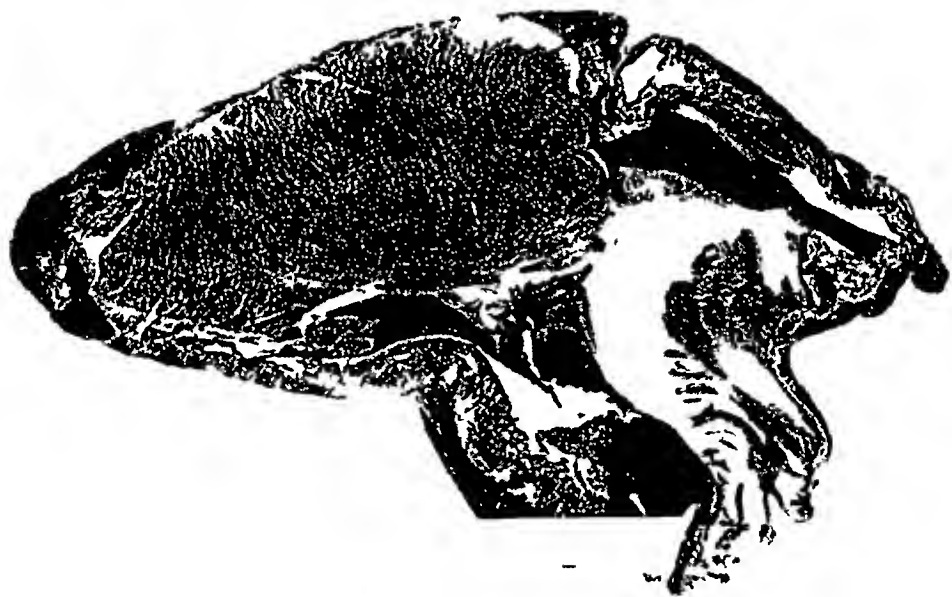


Fig 6—Heart, section through interventricular septum, showing myocardial degeneration and punctate hemorrhages at the apex

Of ten children under 12 years of age, eight had severe attacks and two had light attacks. Six died and four recovered. Although these figures show a high mortality, there seems to be a uniformity of opinion among the local physicians that yellow fever is well borne by children.

## MORTALITY

Nineteen of the fifty cases of the series terminated fatally, a mortality rate of 38 per cent. This was considered about the usual death rate from yellow fever in Guayaquil. The mortality rate in all cases

of yellow fever admitted to the lazaretto from January 1, to August 1, 1918, was 44 per cent

#### TREATMENT

The general principles of the treatment of fevers were followed. No specific or special treatment was carried out in the cases studied. Little or no medicine was given and no conclusions can be based on our experience.

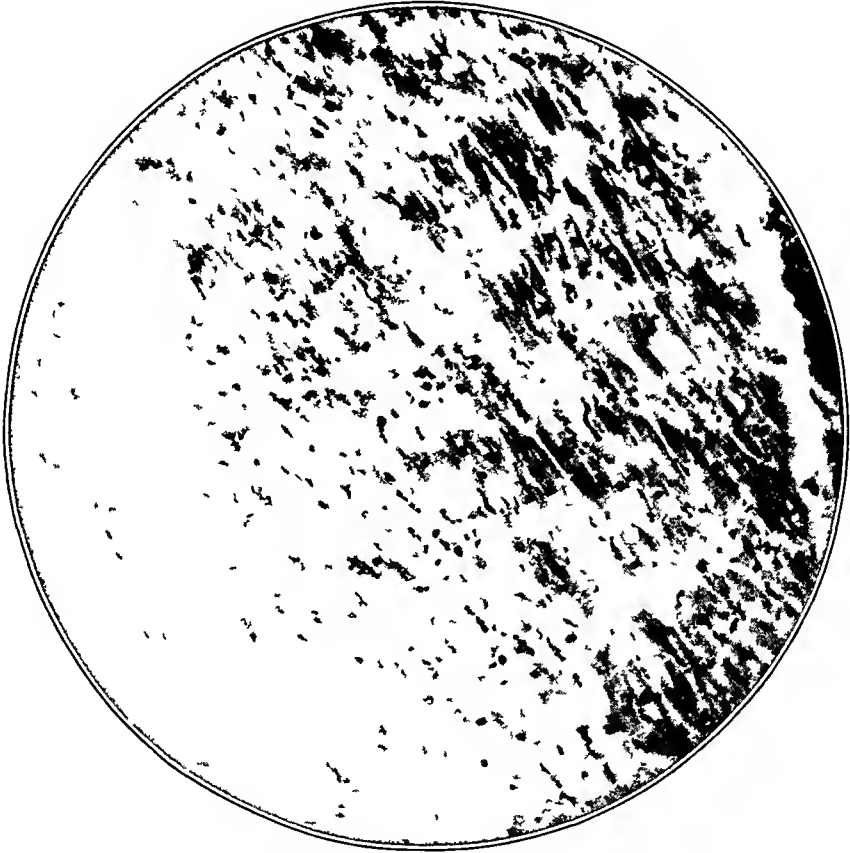


Fig 7—Heart muscle (magnification 140 diameters), showing degeneration and hemorrhage

#### POSTMORTEM FINDINGS

Nine necropsies<sup>3</sup> were permitted and were held as soon as possible after death. The findings were fairly uniform, consisting, in general, of diffuse degeneration of all parenchymatous structures with numerous hemorrhages in all tissues ranging in size from punctate to widespread areas. The tissues were generally dry and intensely jaundiced, the yellow color apparently increasing after death. Exudative changes were absent in all cases.

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3 The microscopic examinations were made by Dr James P Simonds, associate professor of pathology in Northwestern University Medical School

*Heart*—The heart showed from a few to many punctiform hemorrhages on the surface both of the visceral pericardium and the endocardium, apparently more numerous about the auriculoventricular junction, but present in all cases. Punctiform hemorrhages were found in the papillary muscles in most cases. The myocardium was dry, granular, friable, the interventricular septum showing the greatest change. The valves were not affected. In a few cases there appeared to be some dilatation of the right heart, but never to a marked degree.



Fig 8—Lungs, cut sections, showing punctate and confluent hemorrhages

Microscopically, subpericardial and occasionally intramyocardial hemorrhages were found. The muscle fibers were generally swollen, the striations indistinct and in the most severe cases entirely absent in places. The nuclei of the most affected fibers were absent.

*Lungs*—The lungs in all cases except one showed from a few to many hemorrhages varying in size from punctate to extensive areas, on the surface and extending deep into the substances. The lungs were dry, fluffy and bloodless in three cases, while pulmonary edema

with much hypostasis, apparently terminal, was present in six cases. The punctate hemorrhages appearing on the surface of the lungs are found to be the bases of deep hemorrhages into the parenchyma, from  $\frac{1}{2}$  to 2 cm. in diameter, usually few in number, but sometimes grouped and numerous. A few widespread hemorrhages into the lung tissue were observed. Tuberculous nodules were present in three cases, and old pleural adhesions in six cases. Microscopically, no noteworthy changes were seen.

*Liver* —The liver was markedly affected in all cases. The size and shape were usually normal, the edge appeared somewhat rounded in some cases. The surface was smooth, from ocher to deep brown in color, with occasional punctiform subperitoneal hemorrhages. In one case there was a widespread subcapsular hemorrhage on the upper



Fig 9—Liver, cut section, showing uniform fatty degeneration and absence of hemorrhage

surface, in one case all the tissues about the hilus, gallbladder and vessels were markedly edematous. The liver was quite firm and cut with resistance in some cases, while it was soft and friable and offered little resistance to the thumb passed through its substance in other cases. The cut surface was dry, smooth and of uniform color, varying from ocher to dark brown in color. Most specimens appeared to be distinctly fatty. It was remarkable that while hemorrhage was observed in all the other parenchymatous tissues, it occurred in the structure of the liver in only one case. The body of the liver, otherwise extensively degenerated, seemed free from hemorrhage. It is possible that the change in the liver parenchyma had passed the hemor-

rhagic stage at the time of necropsy. Subserious hemorrhages of the liver capsule and about the hilus were frequent.

Microscopically, the most pronounced changes were found in the liver. In the patients that died early in the disease the changes consisted of fatty degeneration, located in the intermediate zone of the lobule. In these areas the cell cords were disarranged, some of the cells had lost their nuclei, and there was hemorrhage into the small necrotic foci. The cells elsewhere in the lobule, and especially those immediately surrounding the central veins, showed evidence of fatty

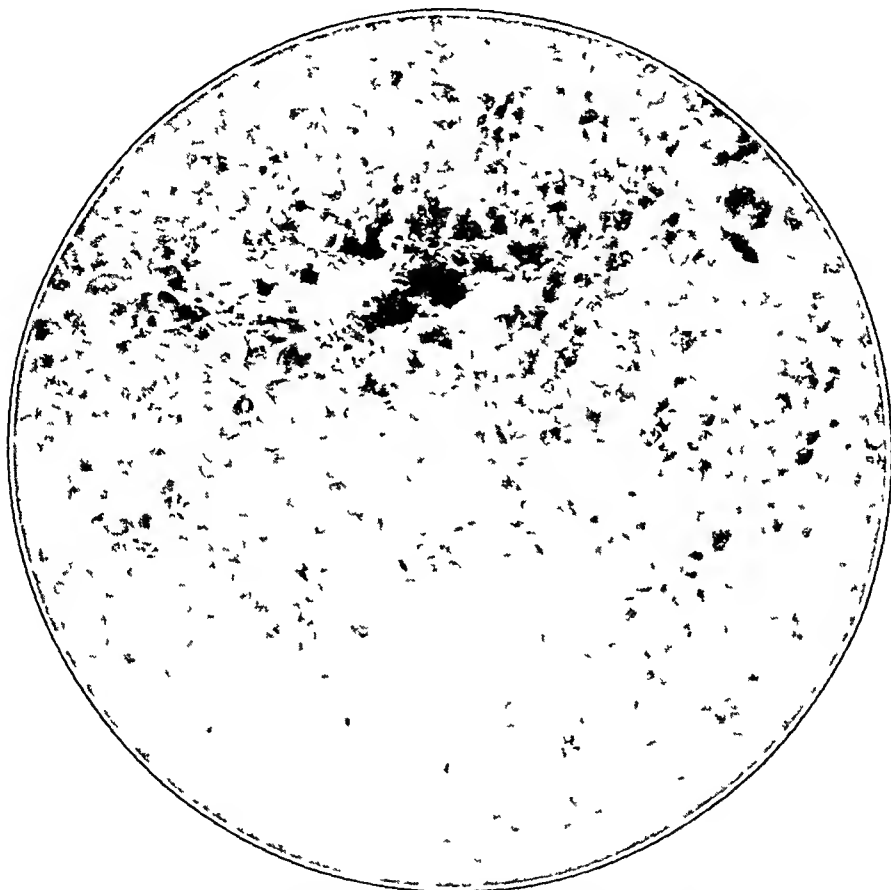


Fig 10—Section of liver (magnification 140 diameters), showing extreme fatty degeneration and necrosis of the epithelial cells with hemorrhage into the necrotic areas. The necrosis and hemorrhage are most marked in the mid-zone of the lobule, the cells about the central vein and those of Glisson's capsule are less affected. The cell cords are disrupted.

change and of swelling. In the livers of patients who died later in the disease practically all of the cells of the lobules showed marked fatty degeneration and infiltration, the cell cords were disrupted, there was much necrosis, especially in the intermediate zone, and there was much hemorrhage into the areas of necrosis. Many of the Kupfer cells contained brown pigment. In one instance in which the patient lived for ten days, the longest duration of the series, there was almost



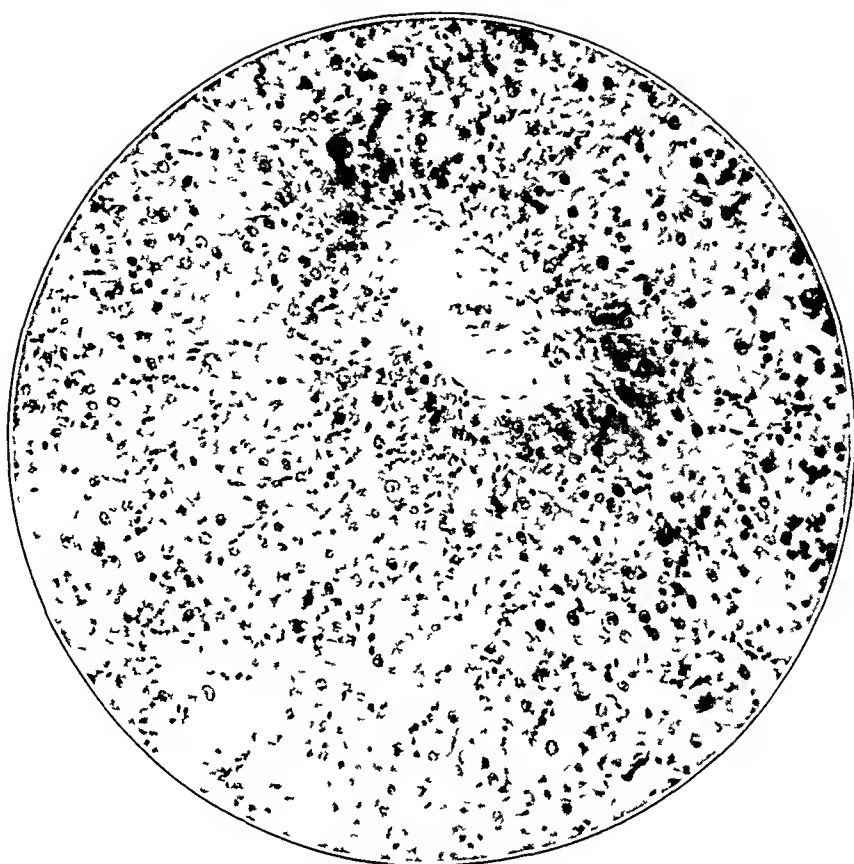


Fig 11—Section of liver (compare Fig 10)

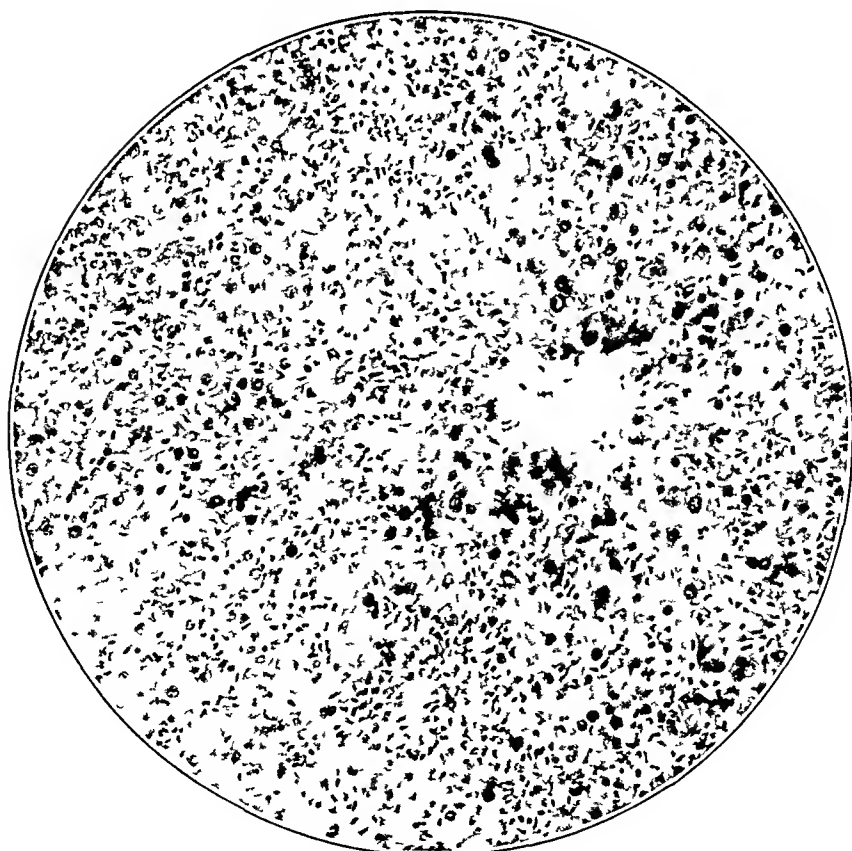


Fig 12—Section of liver (compare Fig 10)

complete necrosis of the hepatic epithelium, only a few poorly staining nuclei being seen at the periphery of the lobules. The structures in the capsule of Glisson preserved their staining qualities.

*Spleen*—The spleen showed no uniform changes. Some specimens were large, triangular and slate colored, interpreted as of malarial origin, others appeared quite normal. Microscopically, the sinusoids in some cases were dilated but empty. There were no areas of focal necrosis.

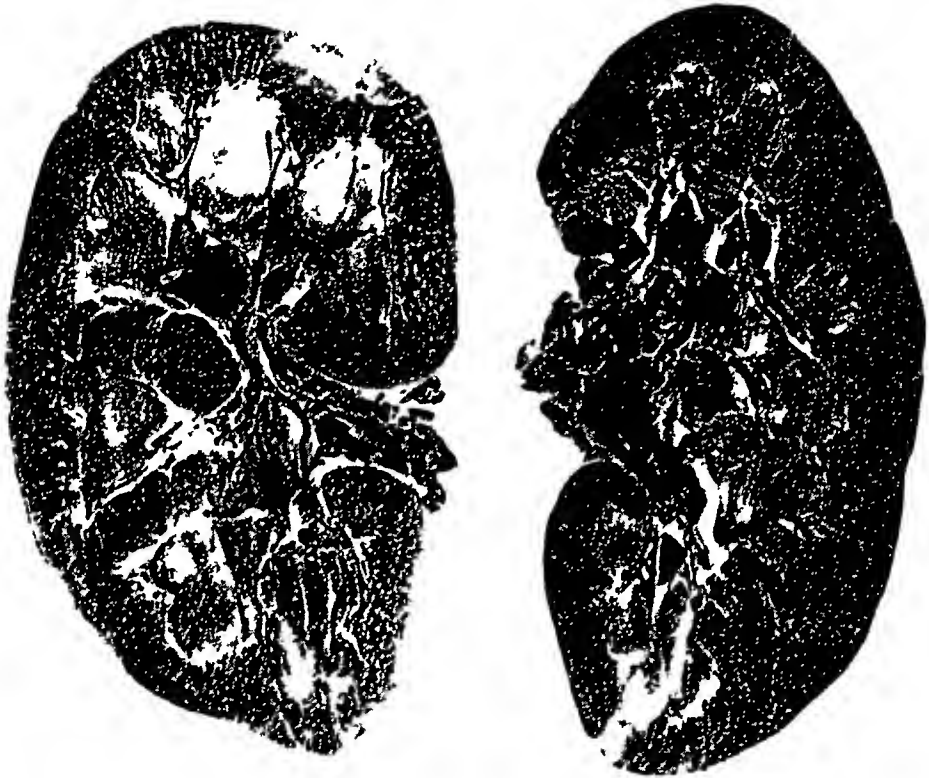


Fig. 13—Kidneys, cut sections, showing acute parenchymatous changes.

*Pancreas*—The pancreas appeared to be not grossly affected.

*Kidneys*—The kidneys were usually enlarged, the capsule stripped readily. The parenchyma was uniformly and diffusely affected, both cortex and medulla appearing swollen in some cases, without any sharp line of demarcation between them. The tubules appeared swollen, some were readily outlined as parallel streaks, some were red and hemorrhagic, others were yellowish in color. The kidneys were all yellow or chocolate colored, hyperemic, sometimes edematous. Seven kidneys showed hemorrhages, punctate to half-dollar size, into the kidney substance, under the capsule or into the perirenal fat. The hemorrhagic areas were usually few in number, although in three specimens they were numerous. In one case there was a large hemorrhage into the pelvis of the kidney.

Microscopically, the most marked changes were found in the epithelium of the convoluted tubules, which showed alterations in structure ranging from cloudy swelling to complete necrosis. In all cases cells could be found which contained vacuoles that probably represented droplets of fat dissolved out in the process of embedding. In general, the amount of necrosis varied with the length of time the patient lived. In those instances in which necrosis was most marked the tubules were filled with a granular mass without any suggestion of cell structure. The glomeruli showed little change other than a moderate hyperemia in some instances. There was occasionally a small amount of exudate in the capsule of Bowman.

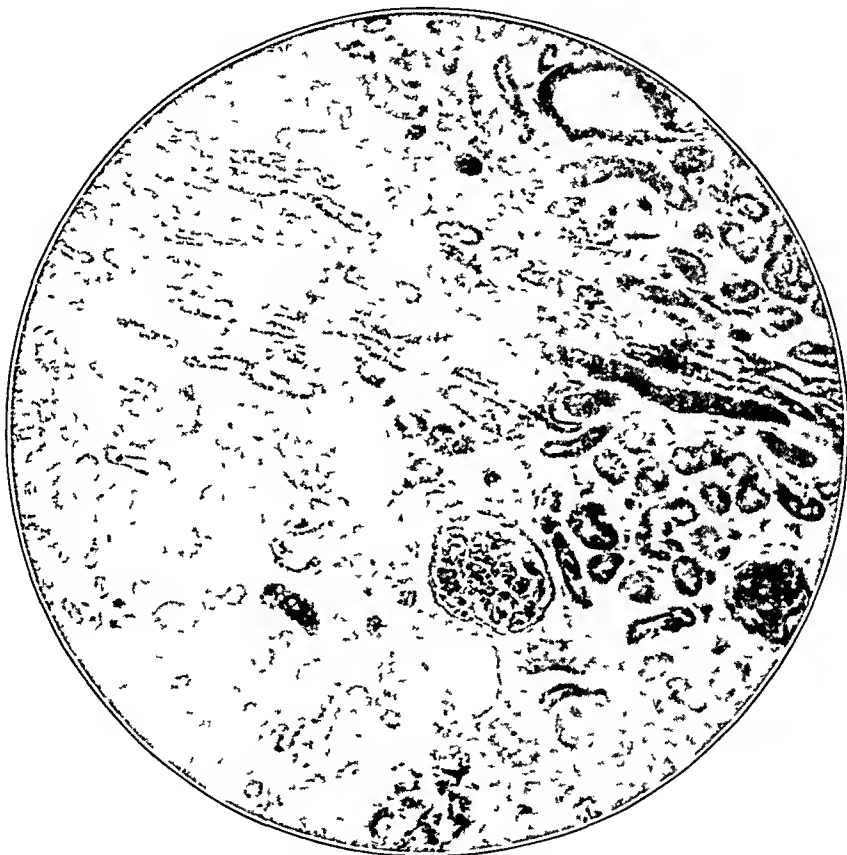


Fig 14—Section of kidney. Intense degeneration of the epithelium of the convoluted tubules, completely necrotic in places and containing granular casts at other points. The epithelium of the collecting tubules is less affected. The glomeruli are hyperemic, some show a slight exudate in the space of Bowman's capsule.

*Stomach*—The stomach showed punctate to extensive hemorrhages into the mucosa, with erosions. Hemorrhages were always more marked at the cardia and lesser curvature than at the pyloric end. "Black vomit" was found in every stomach examined, varying in consistency from a thin "coffee ground" liquid to a sticky, semisolid cho-

colate colored mass which adhered to the mucosa. In two cases there were large subserous hemorrhages near the cardia.

*Intestines*—The intestines in all cases showed diffuse punctiform, often confluent hemorrhages into the mucosa. The intestinal content was a semisolid chocolate colored bloody material. One case showed extensive chronic amebic ulcerations of the sigmoid.

An extensive suprarenal hemorrhage was present in one case, and the mesenteric glands were enlarged and hemorrhagic in two cases. In

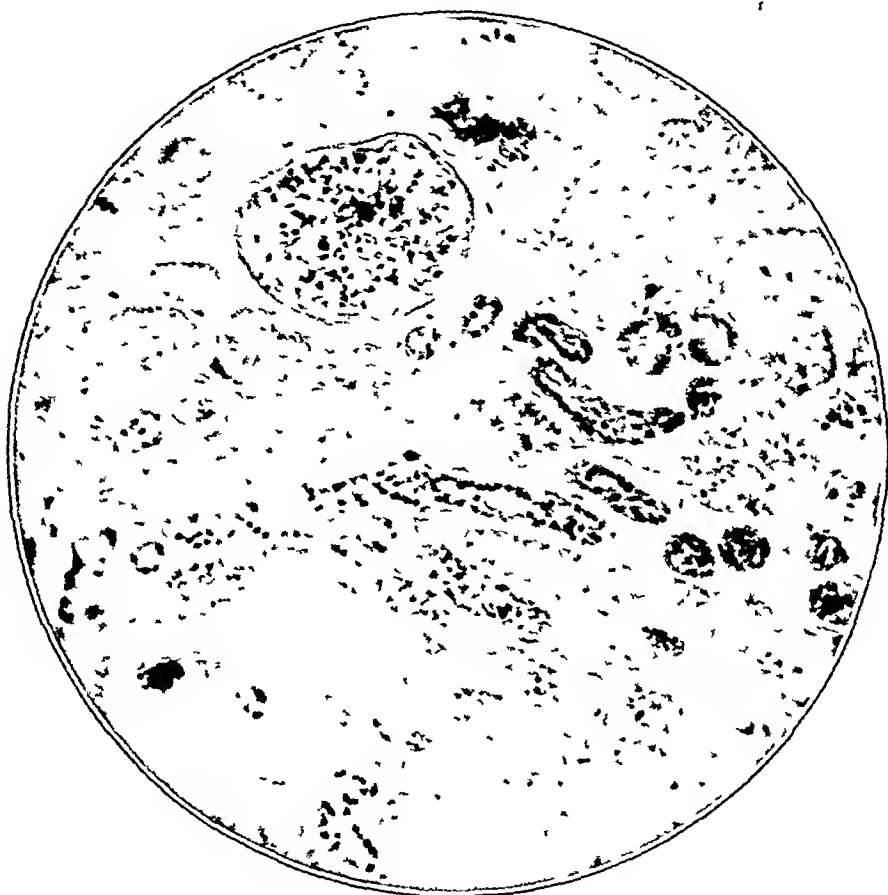


Fig. 15—Section of kidney (compare Fig. 14)

one case there was extensive hemorrhage on the surface of the urinary bladder and in another an extensive hemorrhage on the surface of the gallbladder.

#### SUMMARY

1 The clinical and pathologic findings are summarized from a study of about seventy cases of yellow fever observed in Guayaquil, Ecuador, during the summer of 1918.

2 Clinically yellow fever is similar to infectious jaundice. The differences existing between the two diseases appear to be chiefly those of degree. There is more marked jaundice and less hemorrhage in yellow fever than in infectious jaundice.

3 Although hemorrhage is a usual occurrence in all severe cases, yellow fever is not a true hemorrhagic disease. The hemorrhage apparently follows necrosis of parenchymatous tissues and endothelial cells.

4 The jaundice of yellow fever appears to be of a nontoxic dissociated, hepatic (suppression) type.

5 Death appears to be due to uremia. It is usually preceded by anuria. There is an intense degeneration of the epithelium of the convoluted tubules. The glomeruli and collecting tubes remain relatively free from degeneration.

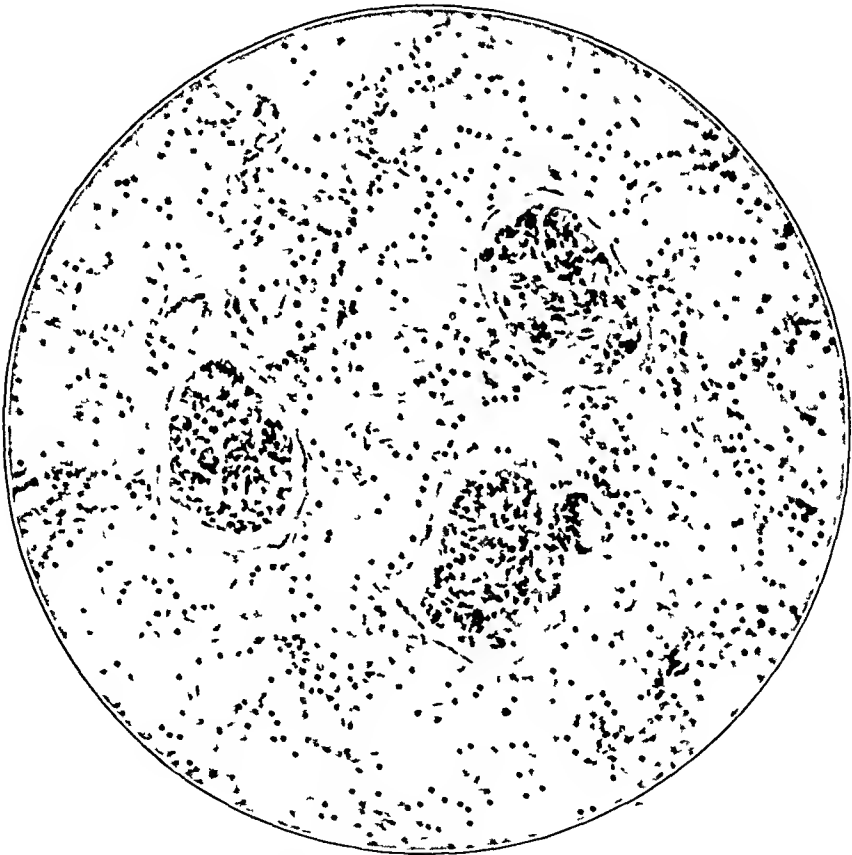


Fig. 16—Section of kidney (compare Fig. 14)

6 Convalescence in all patients who survive is prompt. The complete restitution of all organs to normal is remarkable. No evidences of impaired liver or kidney function remained, although intense parenchymatous changes must have occurred.

#### CASE REPORTS

##### MILD CASE

CASE 12 — Male soldier, aged 25, native of Cuenca, in Guayaquil three years. Had malaria twice previously.

August 18. Third day of illness. Stomach upset. No vomiting. Fever. Aching pain in legs, no headache. Not apparently very ill though prostrated.

Sclerae congested, gums moderately swollen Glands palpable, inguinal large but not tender Epigastric tenderness Lungs heart, spleen, liver negative Red blood cells, 5,224,000, white blood cells, 4,800, polymorphonuclears, 66 per cent, lymphocytes, 22 per cent, large mononuclears 12 per cent, malarial crescents +++ Albuminuria

August 19 Urine albumin +, yellow foam, Gmelin test negative, no casts Slight jaundice and epigastric tenderness Feels better

August 20 Decidedly better, jaundiced, epigastrium tender, liver enlarged Urine albumin  $\frac{1}{2}$  gm per liter, no casts, fluid intake 1,500 c c, output 900 c c

August 21 Condition good Patient comfortable, intensely jaundiced, gums swollen

August 22 Patient less jaundiced, anemic Has lost weight Conjunctivae still injected, gums swollen Albuminuria Blood pressure, 102 systolic, 50 diastolic Convalescent

August 24 Still jaundiced, feels well Red blood cells, 5,424,000, white blood cells 8,600, coagulation time,  $\frac{1}{2}$  minute Discharged (Fig 17)

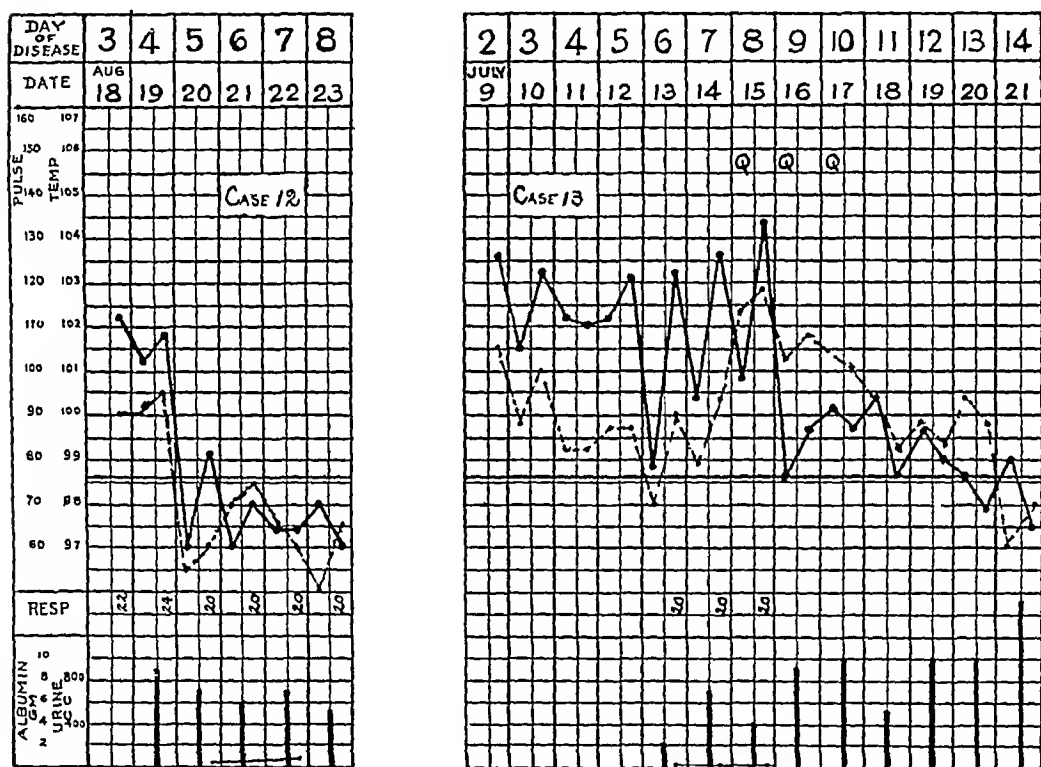


Fig 17—Clinical record of two mild cases (Cases 12 and 13) of yellow fever One of the cases (Case 13) was complicated with a coincident malaria

#### YELLOW FEVER (MILD) WITH COINCIDENT MALARIA

CASE 13 — Male, laborer, aged 18, native of Santa Rosa de Ambato, in Guayaquil fifteen days

July 9 Onset two days ago with headache, nausea fever, no chill Vomited after medicine Slight epigastric pain, jaundiced

July 16 Albuminuria on sixth, seventh and eighth days of disease, none on ninth Physical examination negative except for some enlargement of axillary glands Patient is recovering from yellow fever complicated by malaria No parasites were found in the blood but there was prompt response to two intramuscular injections of 0.5 gm quinin

July 18 Feels well no jaundice Liver palpable one inch below the costal border, not tender

July 20 Feels perfectly well Patient went through a typical yellow fever course but at the end of that time the temperature assumed an intermittent course After three days of intermittent fever quinin was given for three days and temperature fell to normal (Fig 17)

#### SEVERE CASES

CASE 44—Male, servant, aged 16, native of Cualaceo, in Guayaquil three months Had malaria in May

August 9 Ill four days, onset with pain in back, arms and legs, fever, vomited on third and fourth days No bleeding Continuous epigastric pain Stools show ova of trichocephalus Blood pressure 82 systolic, 56 diastolic Red blood cells, 3,864,000, white blood cells, 8,000, polymorphonuclears, 54 per cent, lymphocytes, 32 per cent, large mononuclears, 12 per cent, myelocytes, 2 per cent, no malarial parasites, hemoglobin, 56 per cent

August 10 Intense jaundice, epigastrium very tender, liver swollen, edge rounded, spleen not palpable Severe epistaxis

August 11 Vomited liquid diet Backache and epigastric tenderness Condition improved Intense jaundice, liver small, tender, gums swollen and tender Examination otherwise negative

August 12 Still very ill No change

August 13 Appears better, jaundice less, gums not swollen, epigastric tenderness less, nausea Blood pressure 94 systolic, 58 diastolic Fragility test, 0.42-0.33

August 15 Improved Skin dry, no hemorrhages, jaundice nearly disappeared Physical examination negative Albumin and casts in urine Blood culture sterile

August 16 General improvement but febrile Jaundice slight, recurrence of epigastric tenderness, albuminuria

August 17 Marked epigastric tenderness, albuminuria and a moderate number of casts

August 18 Second rise in temperature Diffuse râles throughout chest, more on left, apparent diffuse bronchitis Heart and spleen negative, liver palpable, tender, muscles tender

August 19 Epigastric tenderness slight Bronchial râles present throughout chest Urine albumin, none, many casts

August 21 Severe bronchitis, coughs frequently Jaundice and congestion of sclerae disappeared Skin covered with sudamina Heart quick, otherwise negative Epigastrium tender

August 23 Lungs show diffuse râles, congestion at base Many pus cells in sputum, no tubercle bacilli found Patient has lost weight

August 26 Red blood cells, 3,232,000, white blood cells, 13,200, polymorphonuclears, 40 per cent, lymphocytes, 24 per cent, eosinophils, 30 per cent, large mononuclears, 6 per cent, no malarial parasites, coagulation time 1½ minutes, large fat bacillus found in blood smear No albumin in urine

August 27 Discharged in good condition

Comment This patient had a severe attack of yellow fever There was a long continued secondary fever with diffuse lung involvement possibly diffuse bronchitis (or punctate hemorrhages?) of unknown origin Terminal eosinophilia not explained Recovery (Fig 18)

CASE 17—Male, servant, aged 20, native of Ambato, in Guayaquil two months

August 17 Onset yesterday, awakened feeling well At 10 a m had general aching of body, then headache, slight fever without chills Today patient is feverish, eyes congested, gums swollen, not bleeding Tongue dry, heavily coated Chest and abdomen negative, slight epigastric tenderness, no muscle tenderness in extremities, no jaundice Urine albumin +, no casts Blood pressure 126 systolic, 58 diastolic Hemoglobin, 65 per cent, coagulation time, 1½ minutes, red blood cells, 4,056,000, white blood cells, 7,800, polymorpho-

nuclears, 81 per cent, lymphocytes, 12 per cent, large mononuclears, 7 per cent, malarial parasites, none

August 18 Patient is feverish, listless, groaning Eyes congested, gums swollen, tongue moist and coated Heart broader than normal, soft systolic murmur at apex Lungs, liver, negative Slight tenderness in epigastrium, no muscle tenderness Urine albumin ++, no casts, many large globular nucleated cells in sediment

August 19 Urine albumin ++, casts +++ (granular and epithelial), many large globular cells

August 20 Seems generally better although fever is high Complains only of headache and some abdominal pain Occasionally delirious but lies quiet

August 21 Urine albumin +++, casts ++, very yellow Patient very ill, delirious with intervals of mental clarity Pulse irregular, gums bleeding, eyes congested Heart and lungs negative, epigastric and general abdominal tenderness Liver enlarged to three fingers below arch

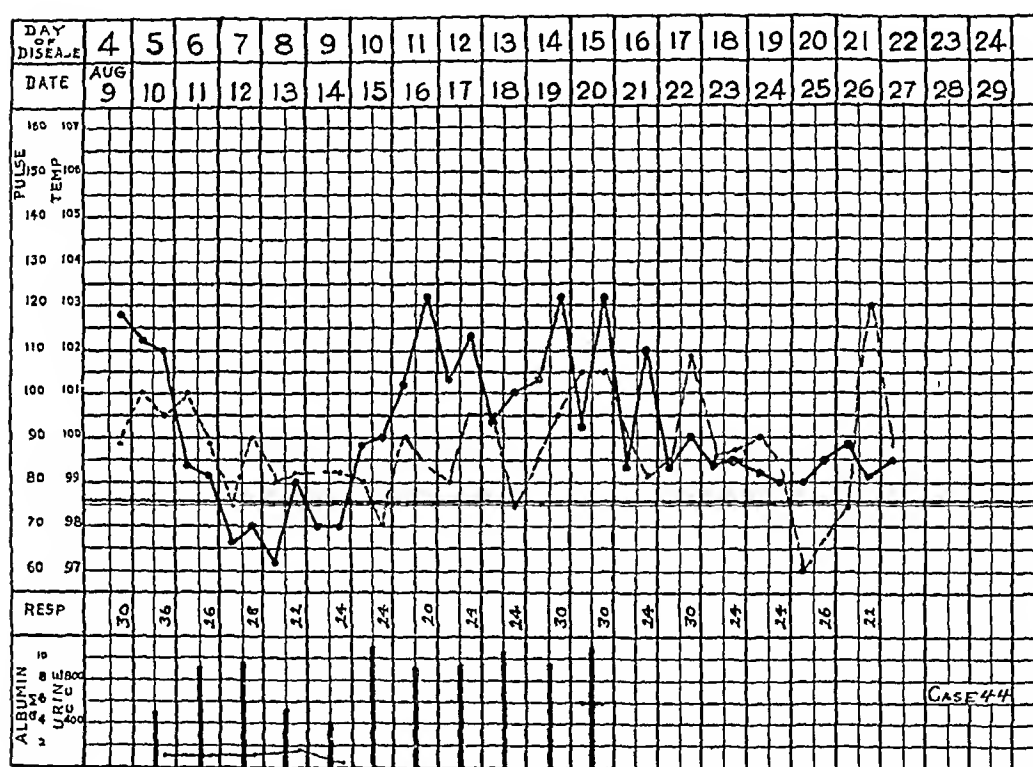


Fig 18—Clinical record of a severe case (Case 44) of yellow fever with diffuse lung involvement

August 22 Oliguria

August 23 Stools clay colored, urine albumin +++++, casts ++, 570 cc voided in twenty-four hours Blood pressure 86 systolic, 58 diastolic Much bleeding from gums, skin dry, intensely jaundiced, relaxed, emaciated Glands, lungs, spleen negative Epigastric tenderness intense, some general abdominal tenderness, no skin hemorrhages

August 24 Mentally clear, much jaundice, less bleeding from gums

August 25 White blood cells, 18,200, very weak, jaundice intense, bleeding from mouth, lies quiet, relaxed Urine contains gross blood in quantity Epigastric tenderness has disappeared, spleen not palpable

August 27 Slightly improved, jaundice intense, eyes congested, gums congested but not bleeding Mucous membranes moist and jaundiced, skin soft and moist, heart and lungs negative abdomen slightly tender, liver enlarged, spleen



apparently enlarged, not palpable Blood pressure 110 systolic, 58 diastolic Hematuria

August 28 Hematuria intense, 920 c c urine voided in twenty-four hours

August 30 Red blood cells, 5,232,000, white blood cells, 7,400, hemoglobin, 58 per cent, polymorphonuclears, 58 per cent, lymphocytes, 26 per cent, large mononuclears, 18 per cent, malarial parasites, none Blood pressure 115 systolic, 62 diastolic, urine albumin +, casts + + +, red cells + Patient is recovering Much muscle tenderness, right elbow very painful on movement, not swollen Emaciated, jaundiced, congestion from eyes and gums has disappeared, sclerae anemic Heart, lungs, liver, spleen, negative Slight epigastric tenderness

September 3 Patient slowly recovering, very weak, hemorrhages have ceased

Comment A severe and prolonged case of yellow fever with intense intoxication and severe hemorrhages Prolonged convalescence Recovery (Fig 19)

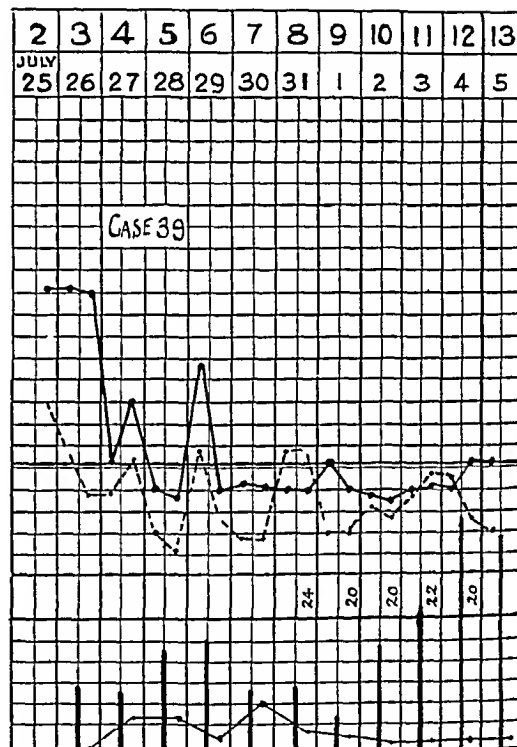
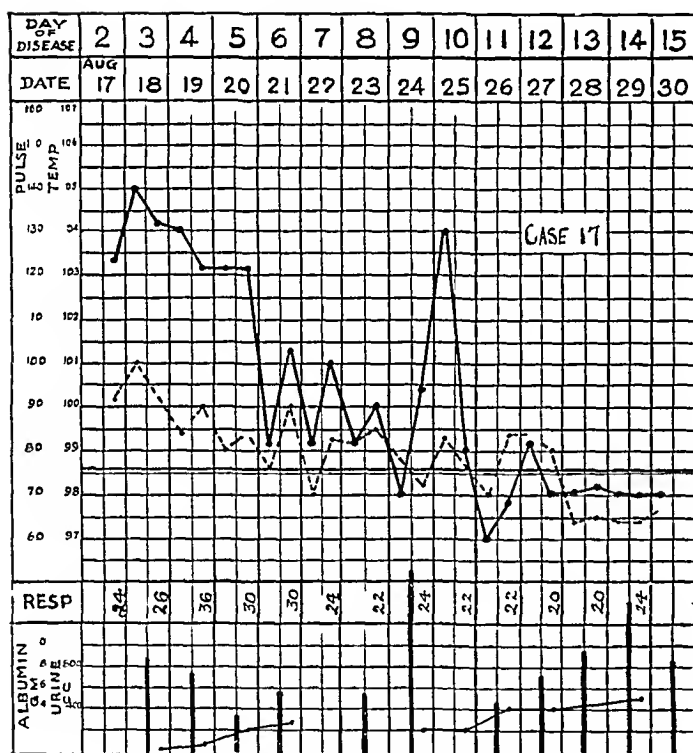


Fig 19—Clinical records of two severe cases of yellow fever complicated by intense intoxication and severe hemorrhages (Case 17) and threatened anuria (Case 39)

CASE 39—Male, policeman, aged 23, native of Ambato, in Guayaquil ten months Had malaria for six days one month previously Chancre +, buboes four years ago

July 25 Taken sick two days ago, vomiting daily, headache, fever and chills, pain in abdomen and upper back One attack of nose bleed—three minutes Constipated Patient is well developed, jaundiced, gums swollen, not bleeding Lungs and heart negative, liver large and tender, spleen large and tender, general adenopathy

July 26 Blood pressure 102 systolic, 68 diastolic Urine albumin + + + +, casts + + + + White blood cells 4,600 Patient very ill, vomiting fever, headache, dizzy, weak, sleepless, area of subcutaneous hemorrhage on penis

July 27 Some improvement, jaundice much more intense Complaints of headache, nausea, vomiting, bleeding gums, thirst, sleeplessness, confusion Blood pressure 95 systolic, 60 diastolic Urine albumin + + + +, casts + + +

July 29 Better though still very sick Daily vomiting, no blood gums bleeding intense jaundice and epigastric pain, pulse 66

August 1 Red blood cells, 4,112,000, white blood cells, 4,200, polymorphonuclears, 63 per cent, lymphocytes, 33 per cent, large mononuclears 4 per cent General improvement, jaundice more intense, gums bleeding, liver large and tender, no evident skin hemorrhages

August 3 General improvement, intense jaundice, slight bleeding from gums Blood pressure 110 systolic, 64 diastolic Liver palpable not tender

August 4 Fragility test 0.39-0.30 Anuria threatened—220 cc in twenty-four hours (improved after forced water intake) Jaundice intense, bleeding stopped from gums Patient is emaciated and weak hungry Red blood cells, 4,032,000, white blood cells 4,800, no malarial parasites Allowed to leave hospital on starting convalescence

Comment A severe case with hemorrhage and threatened anuria Patient discharged weak and intensely jaundiced (Fig 19)

CASE 7—Male, soldier, aged 25, native of Guano, in Guayaquil five years

August 4 Onset August 1, with fever and generalized pain, headache, no chill Yellow vomitus daily, no bleeding Red blood cells, 6,896,000, white blood cells, 3,400, polymorphonuclears, 68 per cent, lymphocytes, 26 per cent, large mononuclears, 6 per cent, no malarial parasites found

August 6 Patient seems very ill, face flushed and jaundiced, eyes congested, sclerae jaundiced Lungs negative heart shows occasional extrasystole, liver area small, tender Blood pressure 84 systolic, 62 diastolic No ova found in stools

August 7 Fragility, 0.39-0.33 Urine albumin, 5 gm per liter, casts, + + + +, water intake 3,850 cc output 650 cc

August 10 Patient very ill although apparently recovering from severe attack of yellow fever, jaundice + + +, gums swollen and bleeding, fetor ex ore, liver large and tender spleen not palpable

August 11 Aching over whole body, weak, relaxed, bleeding from gums, vomiting no blood, liver tender, skin dry Urine albumin, + + + +, casts, + + + +, yellow

August 12 Very ill, jaundice intense, epigastric tenderness very marked, heart irregular, gums swollen, bleeding

August 13 Blood pressure 101 systolic, 70 diastolic All previous symptoms intense, that is, jaundice bleeding from gums, pains in upper arms, abdominal tenderness Fragility 0.33-0.27

August 15 Improved but still very sick, listless, depressed, jaundiced, less congestion of eyes, tongue and mucous membranes moist breath less offensive Heart slow regular liver enlarged, epigastrium tender, lower abdomen not tender, tenderness on deep palpation in extremities Urine albumin, + +, casts + + intensely yellow Blood pressure 112 systolic, 56 diastolic

August 16 Intense jaundice, epigastric tenderness, muscle pain gone still some backache Urine albumin +, casts, few granular

August 18 General improvement, intensely jaundiced spleen edge palpable Pulse 58, blood pressure 110 systolic 68 diastolic

August 20 Urine albumin none many casts, water intake 1,500 cc output, 545 cc Patient better but weak and relaxed jaundiced, epigastrium tender, muscles tender on pressure

August 21 Urine negative Lungs, heart, negative Spleen two fingers below arch general abdominal tenderness no muscular pain

August 23 Coagulation time of blood four minutes Patient convalescent evident loss of weight relaxed jaundice less abdomen slightly tender

August 26 Red blood cells, 5,320,000, white blood cells, 3,600, hemoglobin, 63 per cent, polymorphonuclears, 82 per cent, lymphocytes, 14 per cent, large mononuclears, 4 per cent, no malarial parasites found, coagulation time 1½ minutes Much scaling of skin Urine albumin, +, casts, +

Aug 27 Still jaundiced and weak but apparently recovered Discharged

Comment A severe case with prolonged period of intoxication Recovery complete (Fig 20)

CASE 43—Male, hotel porter, aged 21, native of Cuenca, in Guayaquil four months

August 14 Sick one day with general body pain, fever, some epigastric tenderness Blood pressure 110 systolic, 72 diastolic Red blood cells, 5,840,000, white blood cells, 4,800, hemoglobin, 70 per cent, polymorphonuclears, 72 per cent, lymphocytes, 22 per cent, large mononuclears, 6 per cent, malarial

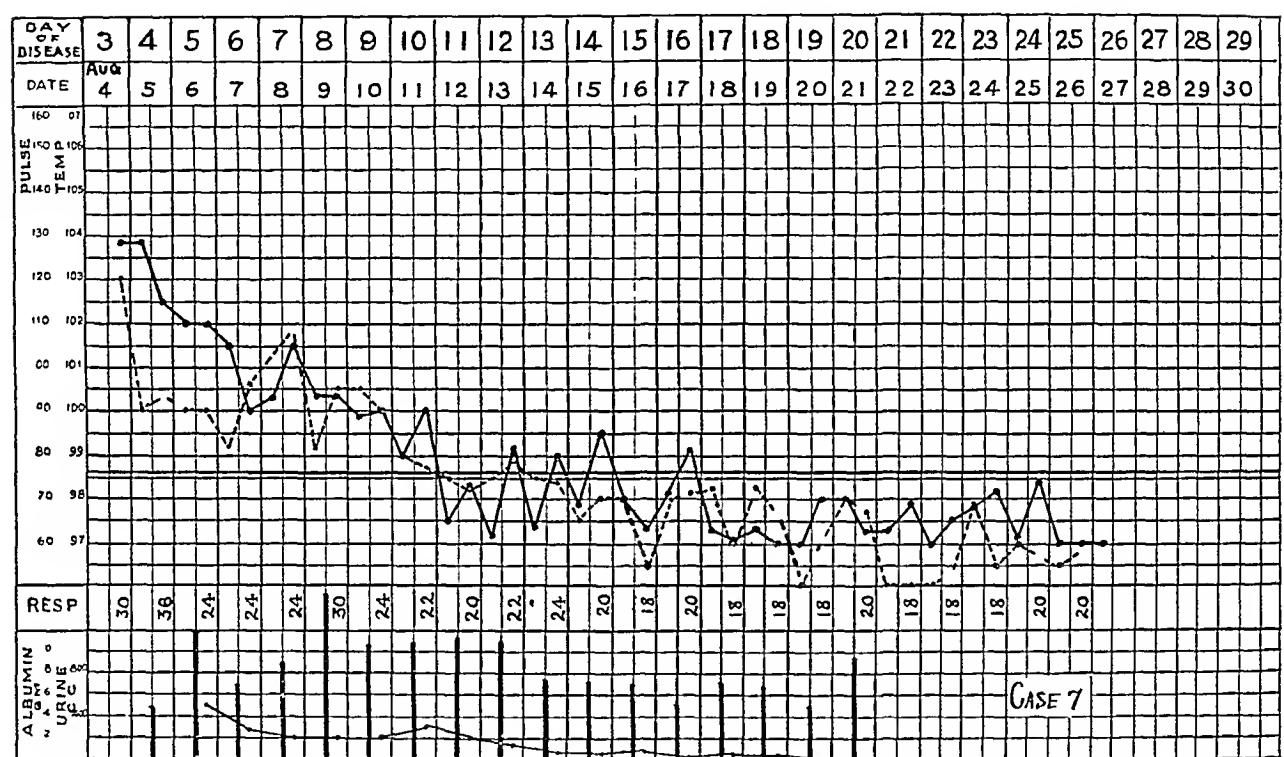


Fig 20—Clinical record of a severe case (Case 7) with prolonged period of intoxication

parasites, none, coagulation time, three minutes Much congestion of sclerae and diffused redness of conjunctivae, tongue thickly coated in plaques, gums swollen—no bleeding General slight adenopathy, not tender Skin hot Systolic murmur over pulmonic area of heart Lungs, liver and spleen negative

August 15 Eyes much congested, no jaundice Urine albumin ++, no casts

August 16 Condition is good, slight jaundice, eyes congested Systolic murmur over base of left heart, lungs negative, epigastrium tender Urine albumin, ++, casts, ++

August 17 Skin is hot, epigastric tenderness marked Ascaris ova found in stools Urine albumin, ++++, casts, ++

August 19 Urine albumin, +++, many granular casts Patient apparently much better, coughing blood, marked epigastric tenderness, lungs and heart negative, intense jaundice, eyes congested

August 23 Some improvement, no vomiting since yesterday Gums bleeding and jaundiced Heart negative, lungs show dulness over right lower posterior lobe, patient coughs General abdominal tenderness especially in epigastrium, some muscle tenderness Blood pressure 89 systolic, 58 diastolic

August 24 Urine albumin, + + + +, casts, +

August 26 Urine albumin, + + +, casts, +

August 27 Weak, relaxed, intensely jaundiced, hungry Eyes not congested, swelling of gums slightly diminished—bleeding stopped No vomiting Pain in right shoulder which is apparently swollen, muscles not tender but joint painful on motion Lungs, heart, spleen and liver negative Left cubital gland enlarged Muscles tender, abdomen tender Apparently much better Blood pressure 98 systolic, 60 diastolic Urine albumin, +, casts, +

August 28 Urine albumin, +, casts, +

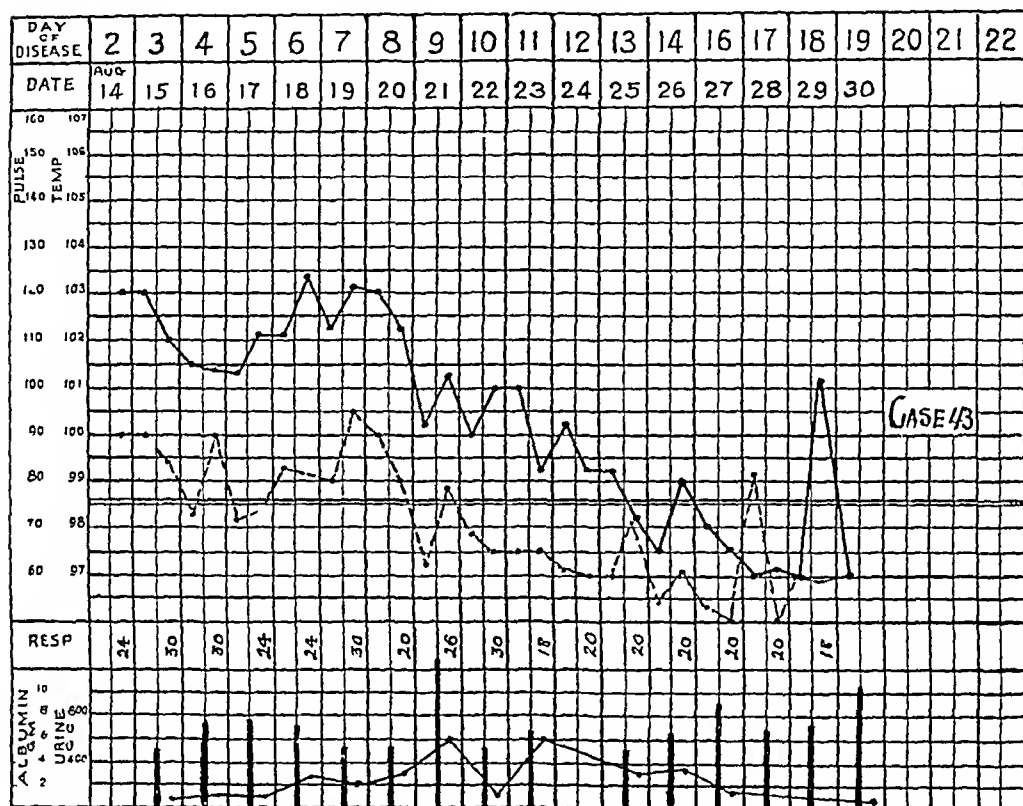


Fig 21—Clinical record of a severe case (Case 43) of yellow fever with protracted fever and hemorrhages

August 30 - Red blood cells, 5,232,000, white blood cells, 8,200, hemoglobin, 74 per cent, polymorphonuclears, 62 per cent, lymphocytes, 16 per cent, eosinophils, 2 per cent, large mononuclears, 20 per cent, no malarial parasites, coagulation time one minute Urine albumin, none, casts, + Marked improvement Intense jaundice, gums and mucous membranes somewhat swollen, right shoulder still painful, epigastric tenderness Findings otherwise normal

September 7 Discharged apparently well although weak

Comment A severe case of yellow fever with protracted fever and hemorrhages (gums, lung, shoulder joint) Recovery (Fig 21)

#### FATAL FULMINANT CASES

CASE 1—Male, jeweler, aged 23, native of Cajamarca, Peru, in Guayaquil two years and three months Had malaria in 1916 and five months previous to present illness

August 23 Ill three days Severe chill in morning followed by headache, general aching and fever Nausea and vomiting daily No hemorrhages At present patient feels weak with pain in legs

August 24 Well developed individual, very sick, quiet, eyes extremely congested, sclerae jaundiced, herpes labialis, tongue coated, edges clear, cervical glands are palpable Heart systolic impurity over precordia Lungs, liver and spleen negative Some epigastric tenderness Blood pressure 122 systolic, 90 diastolic Red blood cells, 6,288,000, white blood cells, 4,000, hemoglobin, 96 per cent, platelets present, malarial parasites not found, polymorphonuclears, 90 per cent, lymphocytes, 8 per cent, large mononuclears, 2 per cent Urine yellow, granular sediment, contained much albumin and casts

August 25 Mucous membranes everywhere much congested, skin dry, jaundiced, herpes drying, hiccup and vomiting, gums swollen, no hemorrhages White blood cells, 3,800, polymorphonuclears, 79 per cent, lymphocytes, 22 per cent In afternoon patient very ill, mentally confused, delirious

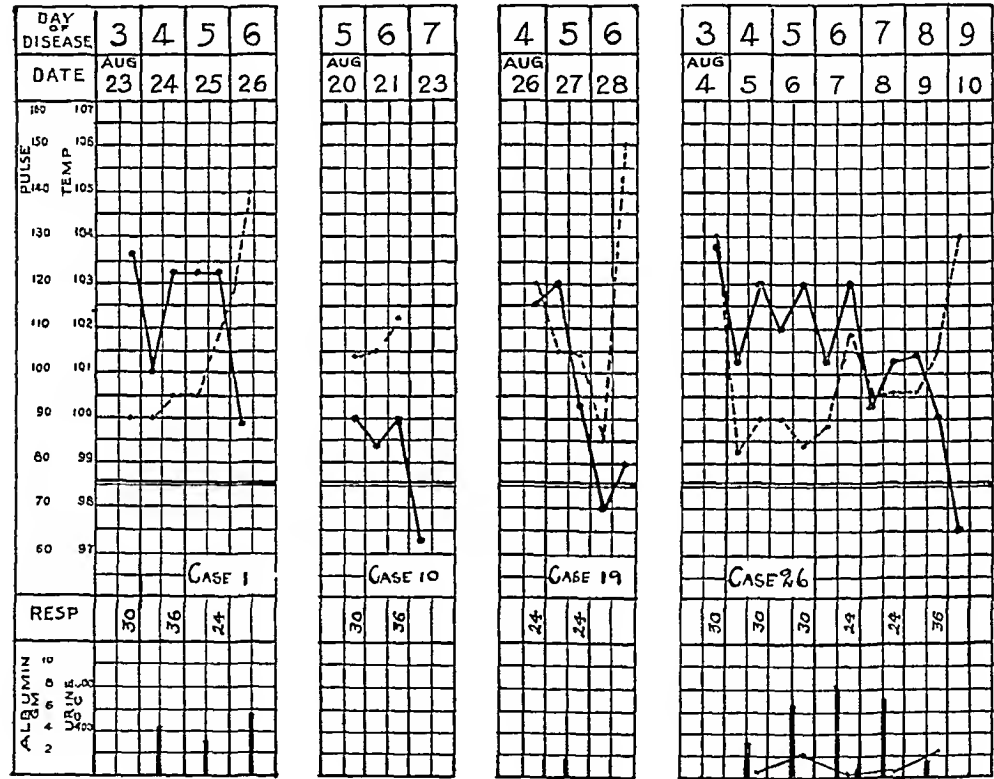


Fig 22—Clinical records of four fatal fulminant cases (Cases 1, 10, 19 and 26) of yellow fever

August 26 Bleeding from gums, much vomiting of black coffee ground material, semiconscious, air hunger, cyanosis, arms cold, pulse feeble, heart rapid (140), lungs negative, bladder distended Urine contained albumin, +++ many hyaline epithelial and granular casts Uremia, coma, death

Comment An intensely sick patient on admission, died on sixth day of disease—an overwhelming infection No necropsy (Fig 22)

CASE 10—Male, servant, aged 10 native of Yaguachi, in Guayaquil two months Has had malaria

August 20 Patient has been ill five days with fever, headache, body pain, nausea and vomiting Is apparently very sick, stuporous delirious Intensely jaundiced, gums swollen and red Heart lungs, spleen negative, extreme abdominal tenderness Red blood cells, 4 392,000, white blood cells, 20 500, hemo-

# ELLIOTT—YELLOW FEVER IN ECUADOR

globin, 74 per cent, polymorphonuclears, 74 per cent, lymphocytes 20 per cent, eosinophils, 2 per cent, large mononuclears, 4 per cent, malarial parasites not found, coagulation time three minutes, blood pressure 98 systolic 62 diastolic

August 21 Wildly delirious, crying out in pain, gums swollen, eyes congested Lungs show many bronchial râles Heart rapid Liver negative, spleen not palpable, area of dulness large Bladder distended, occasional incontinence but no urine procurable Some epigastric tenderness

August 22 Comatose, edema of lungs marked, jaundice + + + +, gums bleeding, intense air hunger White blood cells 49,600

Necropsy, four hours after death Tissues all yellow and dry Lungs contain much fluid, hypostasis, many large hemorrhages into lung tissue, tuberculous nodules in right apex Bronchial glands enlarged, valves normal Liver uniformly light yellow, tremendous degeneration Gallbladder filled, no hemorrhages Spleen large, slate colored Kidneys degenerated, hyperemia, no hemorrhages Suprarenals degenerated and many hemorrhages into tendons with bloody fluid, subserous hemorrhages and many hemorrhages into mucosa, most extensive at cardia Mesenteric glands enlarged (Fig 22)

CASE 19—Male, aged 11, native of Guanando, in Guayaquil two months sick August 27 Sick four days, onset with chill and fever, headache, body aches, legs ache On third day nose bled Continuous fever Patient is very ill and toxic, somewhat stuporous, intensely jaundiced, eyes yellow and congested Heart rapid, lungs, glands, negative, liver enlarged, epigastrium very tender, spleen enlarged one inch below costal arch Skin hot, dry, no hemorrhages, evidently uremic Red blood cells, 3,704,000, white blood cells, 5,000, hemoglobin, 48 per cent, polymorphonuclears, 70 per cent, lymphocytes, 20 per cent, large mononuclears, 4 per cent, myelocytes, 2 per cent, eosinophils, 2 per cent, basophils, 2 per cent, coagulation time, two minutes Malarial parasites, none Stools contain ova of trichiuris trichiura and ascaris lumbricoides, no blood Urine albumin, + + +, no casts, yellow

August 28 Intensely ill, extreme jaundice, wild delirium, relieved by warm bath Died

Comment This child was admitted in extremis, apparently uremic Death No necropsy (Fig 22)

CASE 26—Male, tailor, aged 16, native of Latacunga, in Guayaquil eleven days Had a fever of unknown cause seven years ago

August 4 Onset with chill, then fever, headache, vomited once At present patient is not very sick, there is epigastric pain, abdomen relaxed, liver and spleen negative Skin shows many subcutaneous erythematous areas, a few hemorrhagic, confluent on lower legs Red blood cells, 4,928,000, white blood cells, 3,000, polymorphonuclears, 84 per cent, lymphocytes, 16 per cent, no malaria

August 6 Bloody "coffee ground" vomitus

August 9 Much worse, delirious, jaundiced, gums bleeding, heart rapid Liver area broad, tender Red blood cells, 4,816,000, white blood cells, 7,000, hemoglobin, 88 per cent, polymorphonuclears, 57 per cent, lymphocytes, 33 per cent, large mononuclears, 9 per cent, myelocytes, 1 per cent, malarial parasites, none Coagulation time, one-half minute Blood pressure 109 systolic, 76 diastolic

August 10 Patient comatose, has incontinence of urine, passing large amounts of intensely yellow urine Jaundice intense, gums bleeding, pulse, 150, respirations, 50 lungs negative, liver edge extends a hand's breadth below costal arch, spleen enlarged Death at 2 45 p m Urine catheterized after death contained a very large amount of albumin and of bilirubin

Comment A severe fatal case with hemorrhages and uremia No necropsy (Fig 22)

# PERICARDITIS WITH EFFUSION AN EXPERIMENTAL STUDY<sup>\*</sup>

CHARLES SPENCER WILLIAMSON, M D  
CHICAGO

There can scarcely be any better comment on the difficulty in diagnosing pericarditis with effusion than can be read out of statistics from the postmortem room. Even in institutions where the diagnostic work is admittedly of a high order, the postmortem findings of pericardial exudates entirely unsuspected during life is of not infrequent occurrence. Any one who has been especially interested in the subject must have been struck with the difficulties which are at times encountered in making the diagnosis of such an effusion. Of course, when a well defined friction rub develops in the course of rheumatism, and is followed by a gradual increase in the cardiac silhouette, there can be little difficulty in the diagnosis. On the other hand, in the absence of a pericardial rub, the differentiation between a dilated heart and an effusion may really be very difficult. A considerable number of cases have been reported in which the pericardial sac was aspirated with the expectation of finding fluid, but instead of fluid pure blood came through the needle, in such quantities as to indicate that the heart wall had been punctured. On several occasions I have seen men of distinguished ability do a paracentesis cordis instead of a paracentesis pericardii.

When we examine into the current descriptions of the physical signs in pericarditis, and particularly when we investigate to see on what researches these are based, we meet with a confusion of ideas and statements. While not wishing to discuss the subject from a historical standpoint, a brief statement and criticism of the most important views would seem in place.

One of the oldest views, championed especially by Skoda<sup>1</sup> and his followers,<sup>2</sup> treats of the relations of the heart to the pericardium very

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<sup>\*</sup>From the departments of medicine and anatomy, College of Medicine, University of Illinois

<sup>\*</sup>Although the casts forming the basis of this paper were exhibited at the 1917 meeting of the American Medical Association, my absence in military service has precluded the earlier publication of the paper

1 Skoda Abhandl ueber Auscultation und Percussion, Wien, 1839

2 Oppolzer Vorlesungen ueber die Krankheiten des Herzens, 1867

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NOTE—In each case the left hand photograph is a picture of the cast of the heart itself, the middle photograph is a cast of the corresponding exudate, and the photograph on the right is a section through the exudate on the dotted line. The chest outline shows the relations of the heart and the exudate as seen from the front

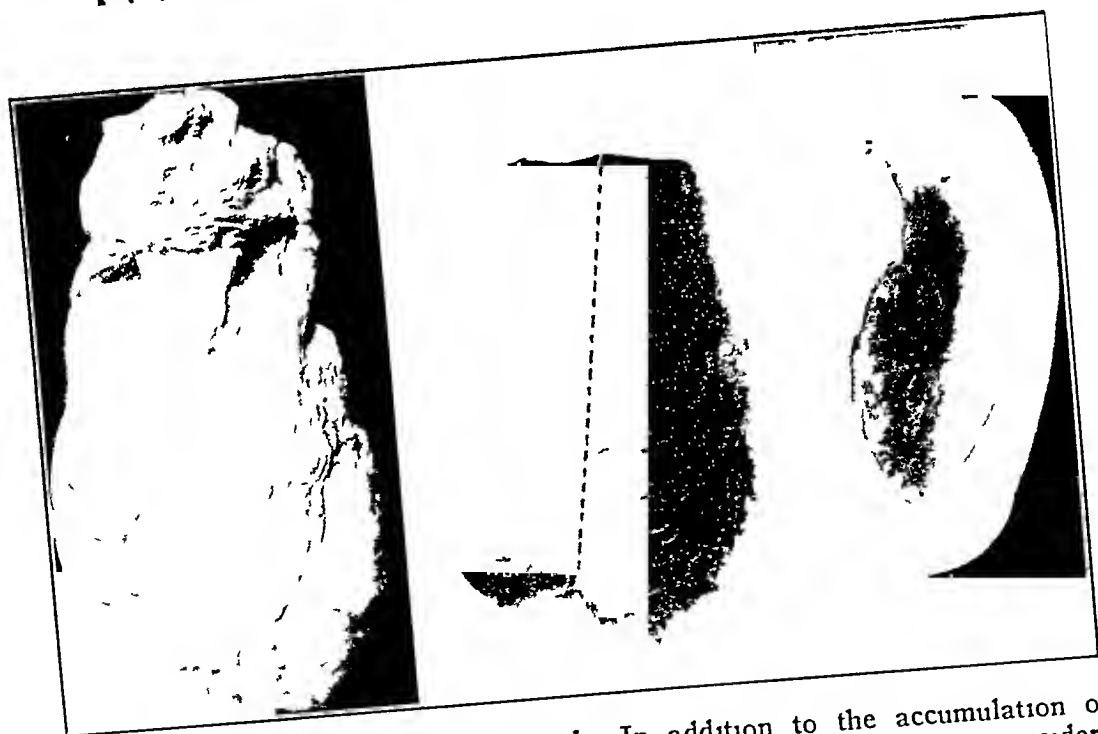
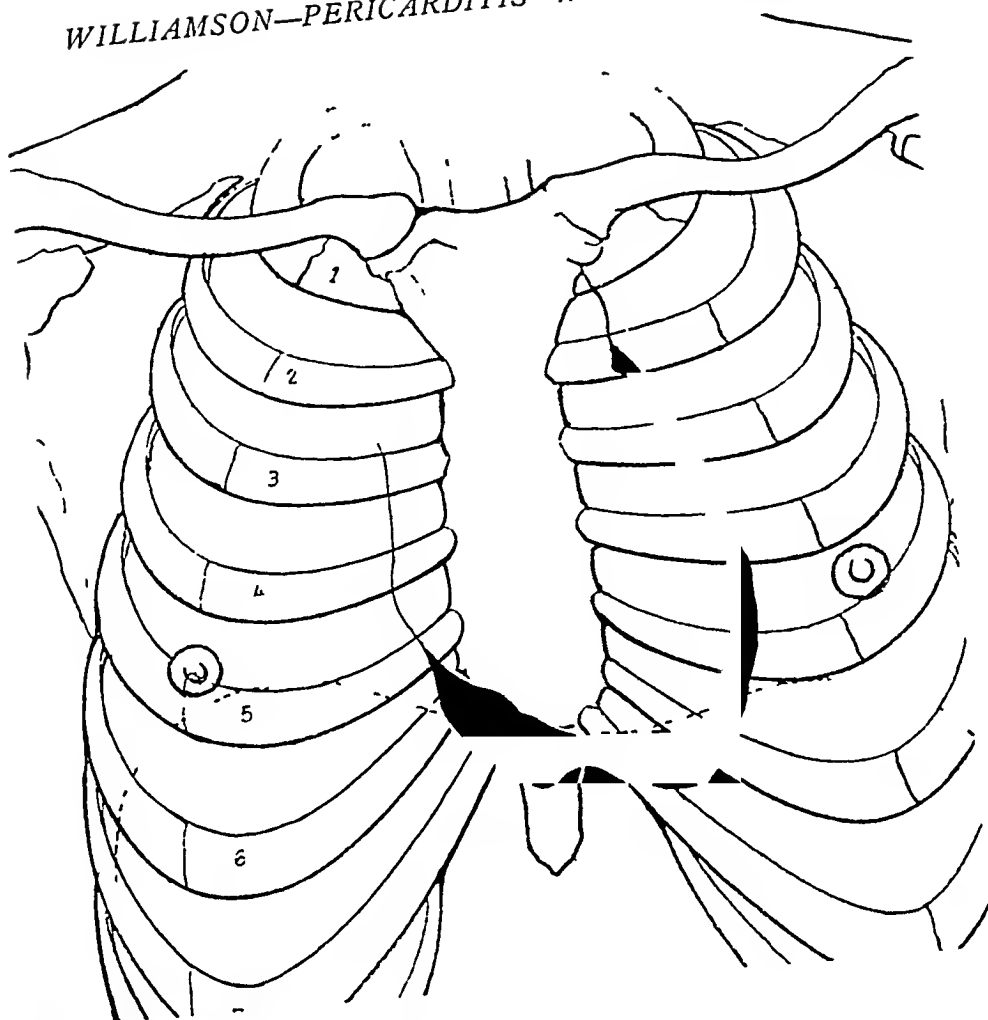


Fig 1 — Exp 4, 300 cc injected In addition to the accumulation of fluid on the diaphragmatic surface and around the apex, there is a considerable amount in front of the great vessels at the base (See note, page 206)



much in the manner of a vessel of water containing a solid body, the specific gravity of which is greater than that of the water. Inasmuch as the heart, with its contents, has a higher specific gravity than a pericardial effusion, it is manifest that on this theory the heart must needs sink in the fluid to the lowest point of the pericardial sac. It requires, however, only a superficial examination to see that the situation is by no means so simple as this view would lead us to believe. To begin with, the analogy of a solid body sinking in a vessel full of water is far from a correct one, especially with small amounts of fluid. The pericardium is not a vessel with rigid walls, but a tough membrane lying with a large part of its surface in close contact with the heart. It is reflected onto the great vessels at the base, and intimately united with the diaphragm at the central tendon of the latter. It will hold about 100 c.c. of fluid before it begins to be stretched. To surround the heart entirely with a layer of fluid of sufficient depth so that one can talk of the heart "sinking" or "swimming" requires an exudate of considerable size, as can readily be seen from our casts. A second and even more important reason why the heart cannot "sink" freely in the fluid, even when this is present in large amounts, is seen in the attachments of the heart. This fixation, as has been shown by several authors, is quite definite and is produced, on the one hand, by the great vessels at the base, and on the other hand, by the inferior vena cava which anchors the heart firmly to the diaphragm. The axis of fixation extends from the inferior vena cava below, to a point a little to the left of the median line above, which may be regarded as the point of application of the traction of the great vessels. It is plain, therefore, that the only extensive movement of the heart which can occur in pericardial effusion, is of the apical portion.

Quite the opposite of this view is held by Schaposchnikoff<sup>3</sup> and his followers. After a series of experiments, using fluid injections, this author came to the conclusion that the heart swims in the fluid and believes that it is held in this position by the elastic traction of the great vessels. This view is strongly supported, he thinks, by the fact that even with large exudates a loud friction rub may be heard over the entire sternum, and at necropsy the heart may be found in close contact with the sternum. Furthermore, numerous operations on purulent effusions have shown that when an incision is made through the chest wall, the heart itself presents in the wound, and that the purulent exudate can only be reached by pushing the heart out of the way. A case of this sort was reported by me<sup>4</sup> and the patient was operated

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<sup>3</sup> Schaposchnikoff, B. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 2: 86, 1897.  
*Rev. de Med.* 2: 789, 1905.

<sup>4</sup> *Med. Clin.* 2: 907 (March) 1917.

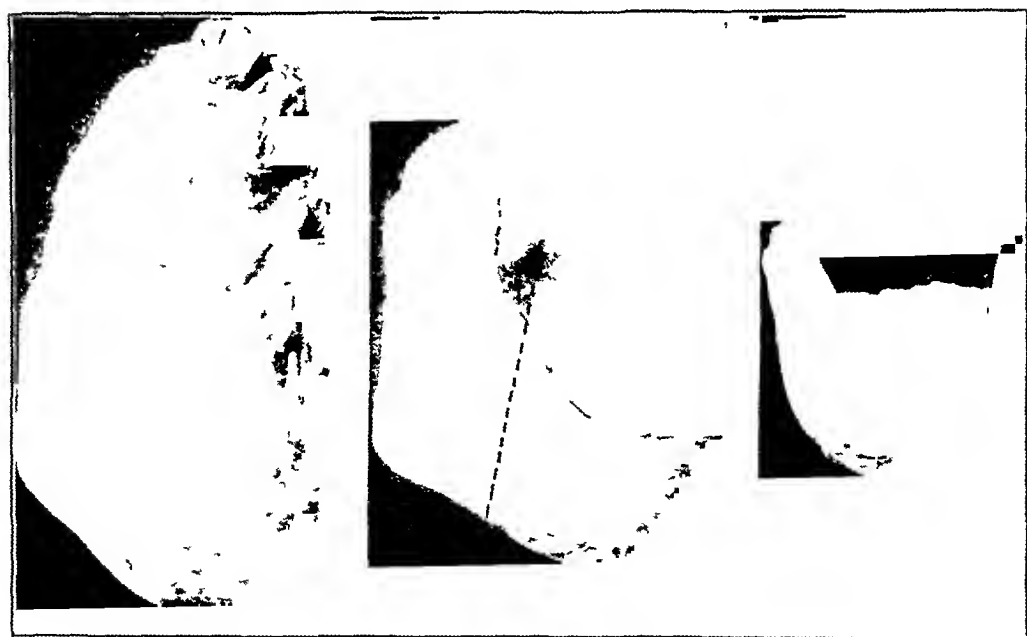
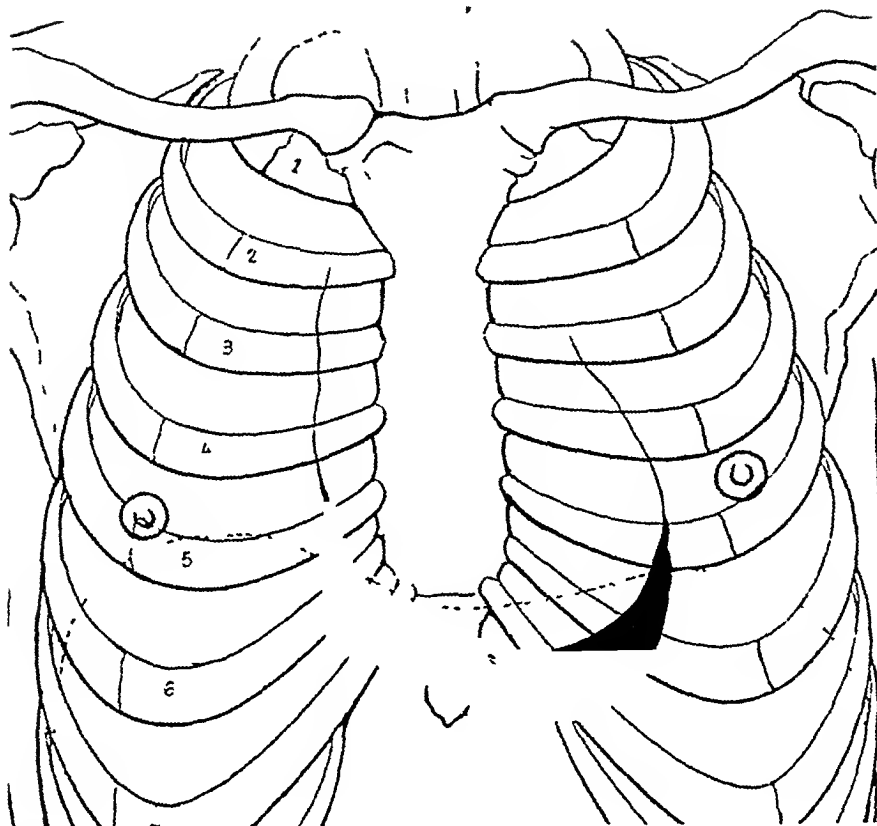


Fig 2—Exp 18, 240 c c injected. A typical small sized exudate is present, confined almost entirely to the diaphragmatic surface (See note on page 206)

on by Dr Kellogg Speed The heart was in close contact with the chest wall, and no pus could be obtained until it was pushed back out of the way and the drainage tube inserted

Curschmann,<sup>5</sup> writing still more recently, holds a view at variance with those of the other observers mentioned This author holds that the more important factor governing the distribution of the fluid, is the small amount of space which normally exists between heart and sternum in front and the vertebral column behind He holds that there is very little room for the heart either to "sink" or "swim" The fluid poured out follows the line of least resistance, and not being able to expand anteriorly and posteriorly in the median line, must, of necessity, spread out laterally toward the pleural cavities, or upward and downward in the direction of the great vessels above and the diaphragm below This author supports his contention by a few cross-sections

Rotch, of Boston, in 1878 investigated the behavior of the fluid by injecting cacao butter into cadavers and determining by percussion the point of first appearance of the fluid The subjects had been previously tracheotomized and the lungs inflated until they corresponded in size with the outlines given by Luschka The most serious objection to Rotch's results is found in that of the sixteen cadavers used—twelve were those of young infants—and that the method is highly subjective Rotch's results, however, have been quoted widely, and his main contention that a dullness in the fifth intercostal space on the right side is the first sign of a pericardial exudate, has been accepted by many writers<sup>6</sup> Ebstein<sup>7</sup> in particular, whose attention was called to this sign by reading Rotch's article,<sup>8</sup> expresses essentially the same thought in another way The angle between the right heart and the liver, the so-called cardiohepatic angle, is normally acute, and he believes that the rounding of this angle is the first clinical expression of a pericardial exudate, and supports this by many illustrative clinical cases Inasmuch as these findings were all obtained by percussion only, his results lie open to the criticism of subjectivity Many experienced clinicians have failed to find either the dullness in the fifth right interspace or the rounding of the cardiohepatic angle in proven cases of pericardial effusion

It is evident that all of these theories cannot be, without modification, reconciled with each other, and with the idea of attempting to bring some order out of the chaos, the experimental work in this research was undertaken

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<sup>5</sup> Curschmann, H Die Deutsche Klinik am Eingang des Zwanzigsten Jahrhunderts **4** 401, 1905

<sup>6</sup> Aporti u Figaroli Zentralbl f inn Med **21** 737, 1900

<sup>7</sup> Ebstein Ueber die Diagnose beginnender Fluessigkeitsansammlungen im Herzbeutel, Virchows Arch f path Anat **130** 418

<sup>8</sup> Rotch Boston M & S J Sept 26, 1878

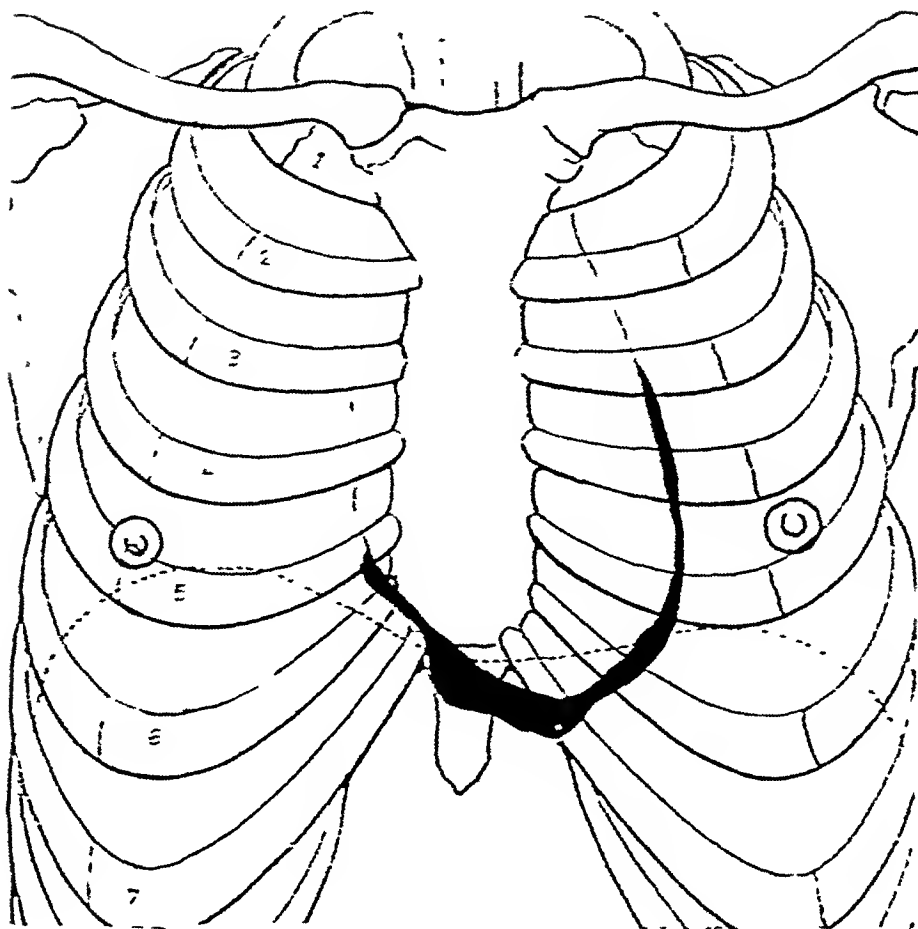


Fig 3—Exp 25. 175 cc. injected. The fluid is almost entirely limited to the diaphragmatic surface and covering the border of the right ventricle. (See note on page 205)

## EXPERIMENTAL WORK

*Methods Employed*—The most important point in any method is that it shall possess a high degree of objectivity. All methods which depend on clinical observations during life lack this almost entirely, and very little progress has been made with these. Much was expected from the applications of the roentgen ray, but however great its usefulness as a diagnostic accessory, it is of relatively small scientific value in this connection, in that it is open to grave errors of interpretation. When used in the ordinary way, namely, with the plate either on the front or back of the chest, it fails entirely to show fluid accumulations either in front or behind the heart.

The most satisfactory methods for experimentation are those which depend on injecting fluids into fresh cadavers. A number of authors have done this after removal of the sternum, which, I believe, entirely invalidates the work, in that it permits the fluid to accumulate in front of the heart by removing the principal obstacle to its accumulation at that point. A far better plan is to make the injection through the central tendon of the diaphragm, since this can be done without materially disturbing the abdominal relations. I selected for the position of the cadaver that most generally used in clinical examination, such as would be represented by the patient being propped on a pillow at an angle of about 15 degrees. Some of our injections were made with the body at an angle of 120 degrees with the thighs, i. e., in the orthopnea position.

After a great deal of preliminary experimentation, I settled on the following technic, which after the requisite manual dexterity had been acquired, proved to be very satisfactory. A small incision was made in the costoxiphoid angle, through which, guided by a finger, a long specially designed trocar was passed. This was made of tempered steel with a sharp stilet provided with a ball on the outside, from three-eighths to one half inch from the point. The purpose of this ball was to prevent penetration to too great a distance. To make the injection, the trocar was thrust obliquely through the central tendon of the diaphragm, the stilet was then withdrawn and a large brass syringe attached to the needle by a screw thread. The syringe I used held 300 c c and was provided with a screw arrangement by which the plunger could be depressed slowly and evenly.

As an injection fluid I settled on a mixture of gelatin and agar-agar made up to the proper specific gravity by the addition of salt. Such a solution, when warm, is perfectly fluid, and under our conditions of experiment, required from one-half hour to one hour to harden sufficiently so as not to be influenced by change of position. To make sure that coagulation would be thorough, we allowed from

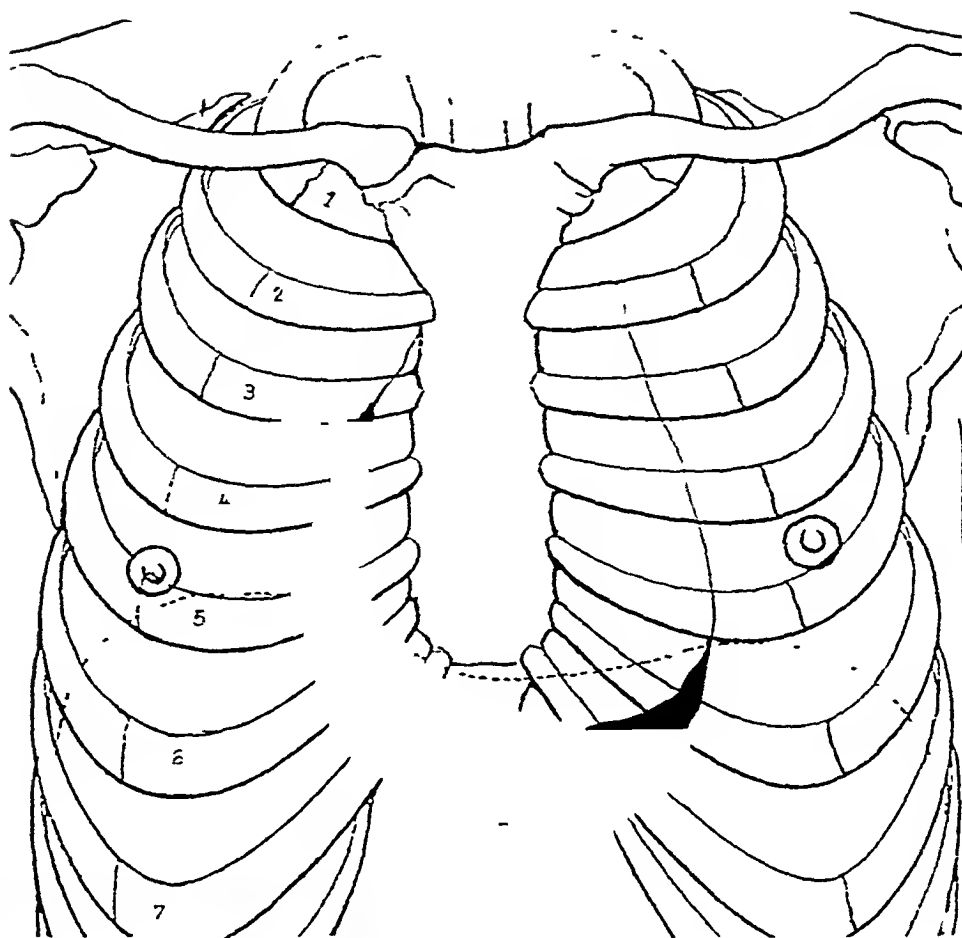


Fig 4—Exp 29, 225 cc injected. The larger portion of fluid is on the diaphragmatic surface, pushing down the liver markedly. A thin tongue of fluid runs along the right margin of the heart. (See note on page 206.)

twelve to twenty-four hours to elapse before making the necropsy. All the information which could be elicited by percussion was obtained as the injections progressed. In each case accurate measurements were taken of the thorax circumference and of the distance between the posterior surface of the sternum and the anterior surface of the vertebral column. At the necropsy the fenestrum was carefully removed, and the exact positions of the heart and exudate were measured, the general outline of the heart and pericardium studied, and then the entire pericardial sac and great vessels were removed in toto. The exudate was sufficiently hard so that it could be handled without fear of breaking. It was immediately taken to the laboratory, placed in a low temperature icebox, and thoroughly frozen. The hearts were then turned over to Mr. Hammer, the modeler of the University of Illinois, whose skill needs no commendation. A cast was made of the heart and exudate together. The exudate was then removed from the heart while the latter was still thoroughly frozen, and a cast and model made of the heart itself. The model of the heart was then placed in the mold first made, and the intervening space filled with a plastic mixture, so that an exact model of the exudate was made. In this manner we finally obtained in each case an exact reproduction of the heart, a similar exact reproduction of the exudate, and lastly, a reproduction of the two together. A very important point relates to the size of the exudate. Most authors have contented themselves with injecting fluids, measuring only the amount as it went in, and assuming that it all remained in the pericardial sac. We did this in the beginning, but found the method grossly inaccurate, since as the injections became larger and the intrapericardial pressure higher, the pericardium would be stripped off from the great vessels posteriorly and large amounts of it would escape into the mediastinal and pleural cavities. We lost a large number of experiments in this way, and even in perfectly fresh cadavers, we have not succeeded in introducing larger amounts than 655 c c without producing a rupture of the pericardium, or what is more commonly the case, stripping it off the great vessels posteriorly. The exudates were measured entirely by the method of displacement, which gives, of course, absolutely accurate results.

The casts were then photographed in the studio of a commercial photographer with a large camera which was arranged vertically. The casts were placed in their proper position on the floor of the platform, using a long focus lens so that the distance was sufficiently great to prevent appreciable distortion. All of the casts were photographed at one sitting, the camera left set up, the casts were then sawn through and the cut sections brought back and photographed under precisely the same conditions.

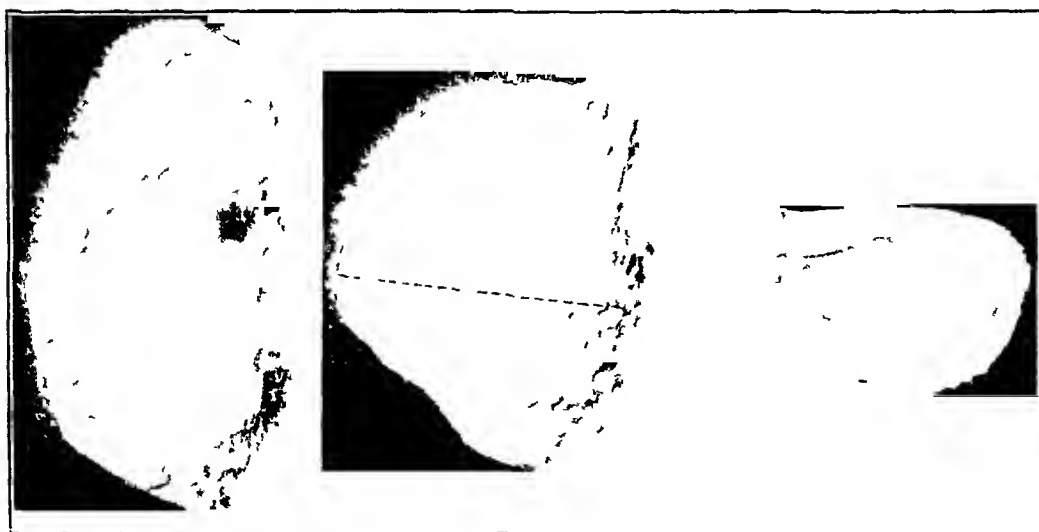
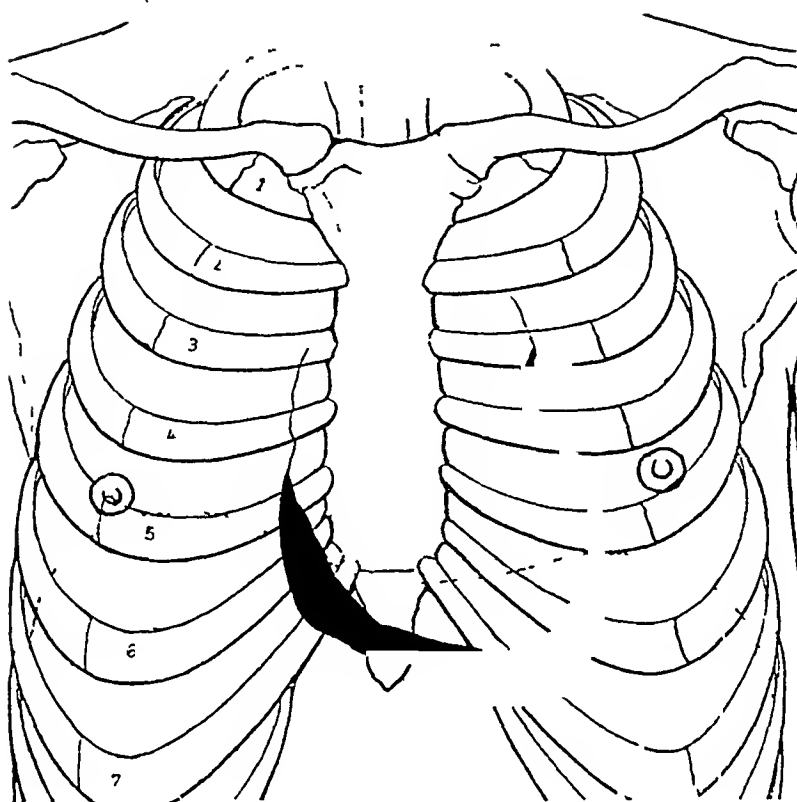


Fig 5—E\p 32, 300 cc injected This shows the greater part of the accumulation of fluid around the apex and diaphragmatic surface (See note on page 206)



In order to be able to show accurately the outlines of the hearts and exudates on a chest outline of exactly the same relative size, the following method was adopted. First, I determined the exact amount of reduction of the photograph by comparing the size of the cast with the size of the corresponding print. From the measurements taken of the cadavers an average was struck, and all that it was necessary to do was to obtain a chest outline bearing exactly the same proportion to this average measurement as the photographs of the casts did to the casts themselves. A chest outline was then made to this exact scale. By means of tracing paper, the outlines of the heart and exudate were obtained from the photographs and these placed in position on the chest outline. The accuracy of this was insured by always leaving a considerable length of the great vessels at the base so that there could be no question as to the precise position. In addition to this, the data obtained by the measurements taken at the necropsy were at hand. For invaluable assistance in this work I am indebted to Mr Thomas Jones, the artist of the anatomic department of the University of Illinois.

In this way thirty-three cases were studied, and I believe that the method possesses advantages over previously used methods in that a great degree of objectivity was attained. The casts are substantial and can be examined and measured in every conceivable way. Particularly, do they show the relations of depth in a way impossible by means of the roentgen ray. My experiences lead me to believe that far reaching conclusions drawn from percussion findings, after the injection of varying amounts of fluid, are apt to be highly fallacious. It is self-evident that percussion cannot possibly give any idea of depth, and affords but a very imperfect idea, if indeed any, of fluid which accumulates between the heart and diaphragm, or in any position where the flatness of the fluid is not in contrast with the resonance of the lung.

*Results Obtained*—The cases have been divided quite arbitrarily into two groups. The first group includes all those cases in which the exudate measured 350 c c or less, the second group included those cases in which the exudate measured between 350 and 655 c c, the latter being the largest injection. In spite of a large number of injections with larger amounts of fluid, it was invariably found that there had been a small rupture of the pericardial sac, and that much of the fluid had escaped. This is in accordance with the experience of most authors who have made carefully controlled injections.

These two groups will be referred to as the small exudates and the medium sized exudates, respectively. Turning to the first of these, the small exudates (Experiments 4, 18, 26, 29, 32, Figs 1, 2, 3, 4 and

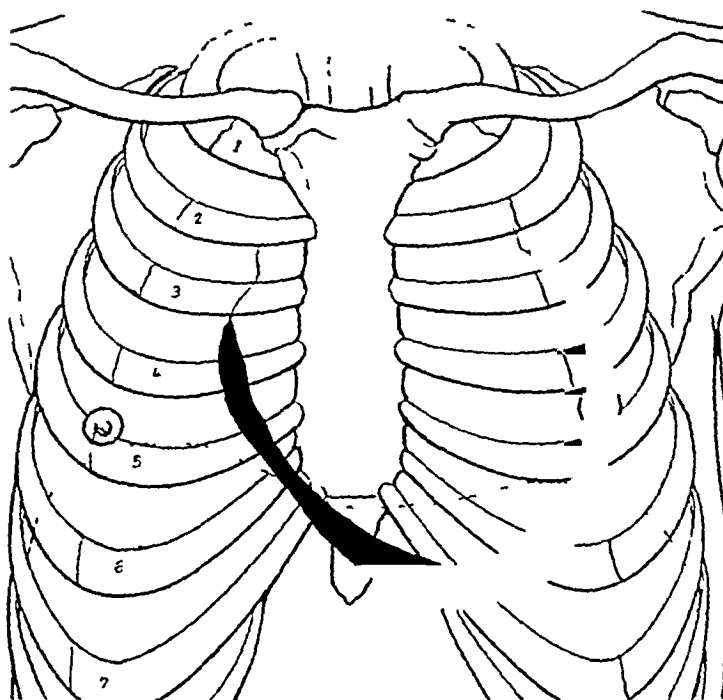


Fig 6—E\p 1, 460 cc injected Weight of heart 530 gm The fluid is almost entirely confined to the diaphragmatic surface The front of the heart is uncovered This figure illustrates well the point that with large hearts the fluid does not collect in front (See note on page 206)

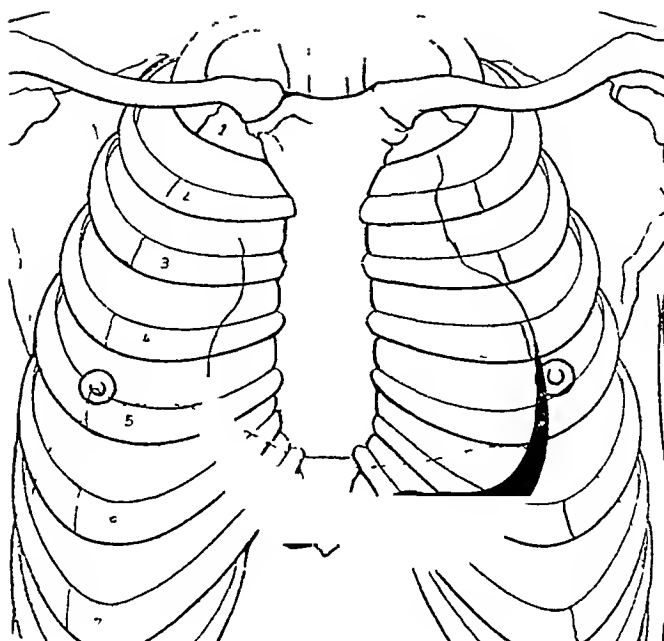


Fig 7—Exp 12, 475 cc injected The heart was very large, weight 550 gm In spite of the large exudate, the entire anterior surface of the heart remained uncovered (See note on page 206)

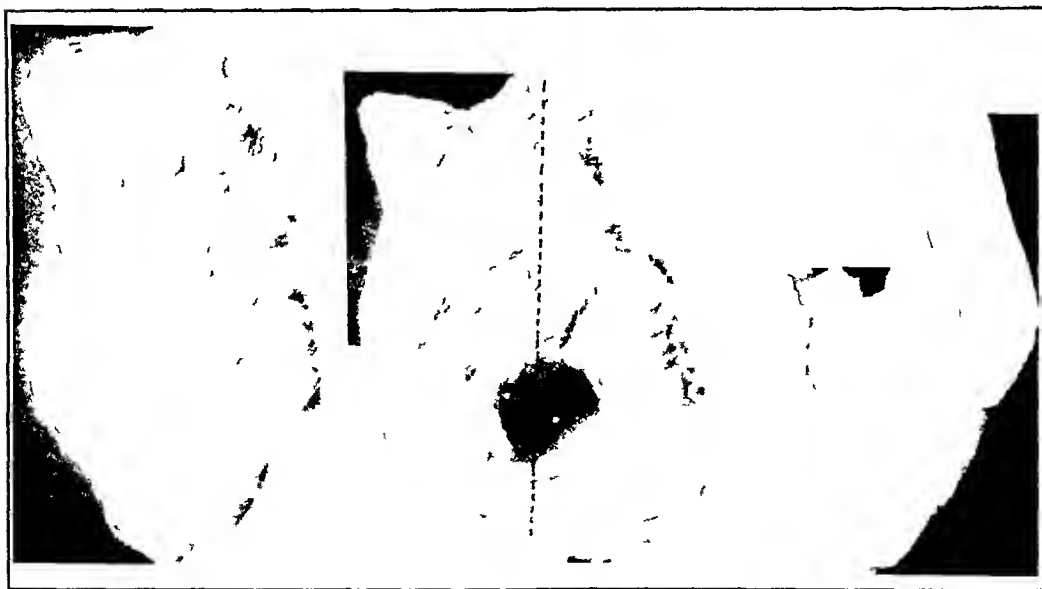
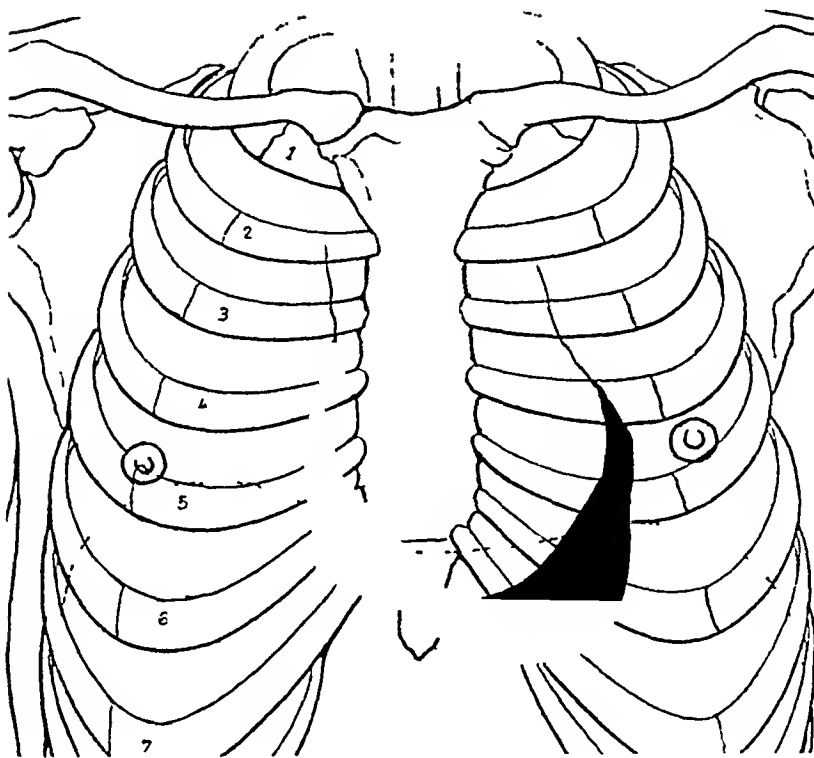


Fig 8—Exp 16, 425 cc injected. The front of the heart is not covered by fluid, which is found in about equal amounts on the diaphragmatic surface and in front of the great vessels. (See note on page 206.)

5), let us see where the exudate first collected. It is impossible, for lack of space, to reproduce all the photographs. The ones shown are selected as being typical. It requires but very slight study of the photographs and their cross sections to see that in every instance the major portion of the exudate collected in the angle formed by the anterior chest wall and the heart, and to even a larger degree between the right ventricle and the diaphragm, pushing down the latter. In every instance the apex was covered with at least as great a thickness of fluid as the remainder of the diaphragmatic surface. It should be noted that the position of the cadaver makes but little, if any, difference, since in experiments 26, 29 and 32 (Figs 3, 4 and 5) the cadavers were injected in the upright position, the others were injected in the normal recumbent position.

A careful inspection will show that the liver was materially depressed in practically every case, especially the left lobe, as it presents in the chondroxioid angle. On performing the necropsies the most striking thing noted was *this pushing down of the diaphragm, and with it the left lobe of the liver*. This depression of the left lobe of the liver is more in the nature of a rotation downward than a pushing down of the liver en masse.

A careful inspection of the angle formed by the pericardial exudate and the liver, shows that *in not a single case was this angle obtuse, nor were we able in a single case to demonstrate to our satisfaction a sufficiently marked dullness in the fifth right interspace to be of diagnostic value*. On the other hand, in spite of the fact that in several of the cases the exudates covered the great vessels with a fairly thick layer (as in Experiments 4 and 16, Figs 1 and 8) we were not always able to determine this with certainty before making the postmortem. The depth at which the great vessels lie, and the readiness with which the exudate in this position may be covered by the lungs, is probably the explanation.

Turning now to the group of medium-sized exudates (Experiments 1, 12, 16, 19, 25, 27 and 28, Figs 6 to 12) the heart is found relatively more evenly surrounded, and as the exudates grow larger in amount, the anterior surface becomes more frequently covered. In this connection it is necessary to call attention to the fact that in all work on the cadaver, inasmuch as there is no pressure due to the blood in the heart and great vessels, these structures collapse under a much smaller pressure than they would in the living subject, and in so doing become flattened out laterally and, possibly to a very slight extent, longitudinally. This is quite plainly shown in a number of the cuts, giving the appearance of the heart being relatively too large. Intravital, the

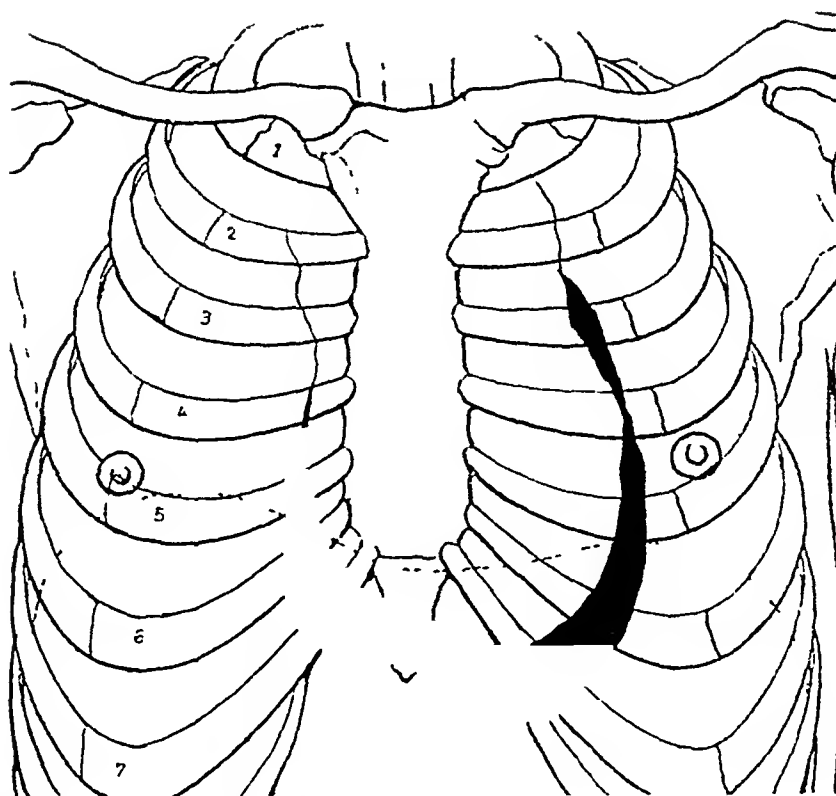


Fig 9—Exp 19 435 cc injected The fluid is largely confined to the diaphragmatic area Note that a large part of the front of the heart is not covered by fluid Only a small amount of fluid covers the great vessels (See note page 206)

heart would collapse much less readily, and fluid would less readily accumulate in front of the heart

An especially careful study was made of the position of the apex beat and we reached the conclusion that there is no change whatever in its position, except, possibly, a very slight displacement downward. This is, however, of too small an extent to be of any clinical moment. In some of the cases the pushing down of the diaphragm and with it the liver, is extremely marked (Experiments 16, 25 and 28, Figs 8, 10 and 12). It is well to emphasize that this is the outstanding feature, as disclosed by the necropsies in the great majority of the cases. In all of these cases the apex is covered with at least as thick a layer of fluid as is the diaphragmatic surface. In this group of medium sized exudates one may repeat word for word what was said of the smaller exudates, namely, *that in not a single case was the cardiohepatic angle obtuse, nor were we able in a single case to demonstrate to our satisfaction a sufficiently marked dullness in the fifth right interspace to be of diagnostic value*

One of these cases, Experiment 27 (Fig 11), occupies an unique position, in that it came from an actual case of pericarditis with effusion, developing in the course of a pneumonia of the right upper lobe. The patient died suddenly and rather unexpectedly, and within a few minutes after death we aspirated through the diaphragm in the usual way and withdrew all the fluid we could obtain, namely, 270 c c, and immediately injected exactly the same amount of agar solution. It may be noted that the total amount of the exudate as determined by the measurement of the cast was 405 c c, indicating the difficulty of removing all the fluid. This case is an extraordinarily instructive one, in that the pressure conditions were precisely the same as during life. An inspection of the great veins and auricles especially shows them to be flattened out, and this must have been their condition in the last moments of life. In the light of the work of François Franck<sup>9</sup> and Starling,<sup>10</sup> one cannot help but believe that death in this case was actually the result of excessive pressure, and that had the fluid been aspirated, the pressure factor at least would have been removed. In this particular case a thin layer of fluid covered the heart in front, and extended far up onto the great vessels. I examined the patient about one half hour before death and dictated the following note on the heart: "Apex indistinct, dullness extends outside the midclavicular line in the fifth interspace, and upward along the great vessels on the left edge

9 Franck, François. Recherches, etc, Gaz hebdomadaire de médecine 29 1877

10 Starling. Some Points in the Pathology of Heart Disease, Lancet 1 569, 1897

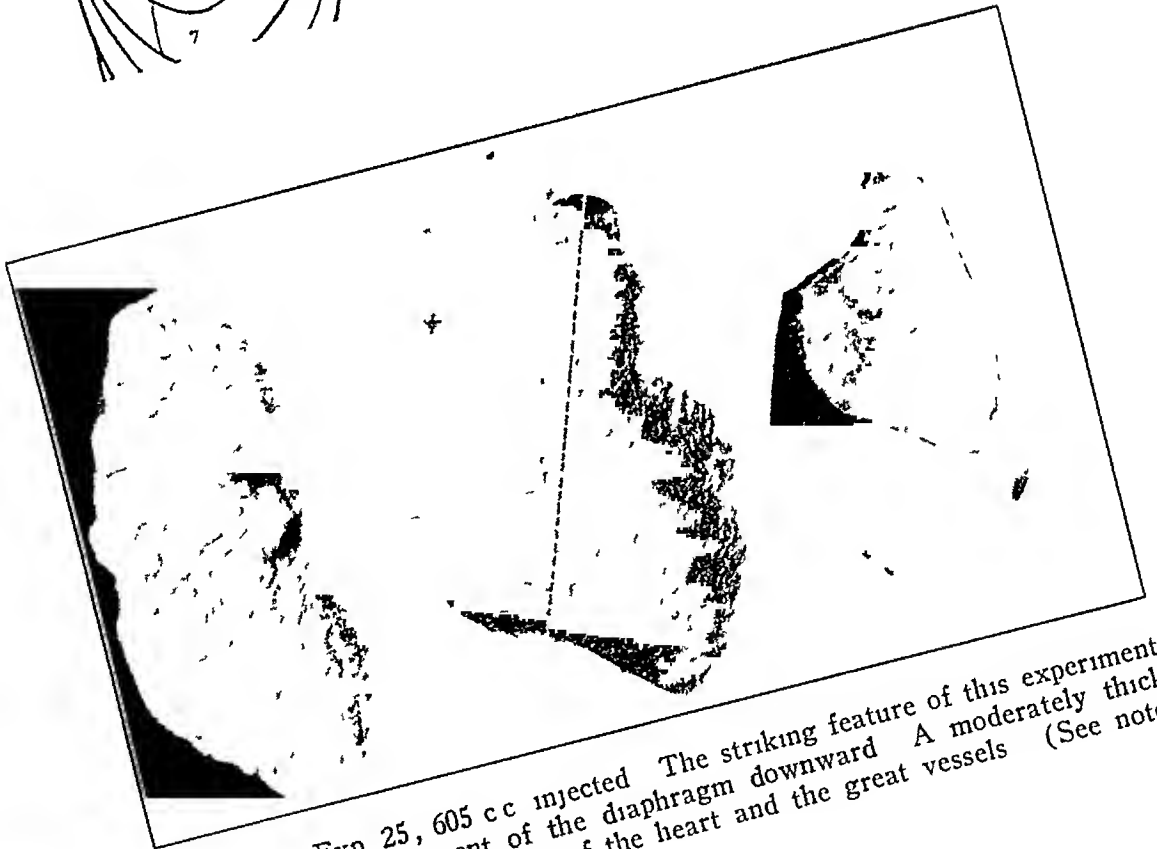
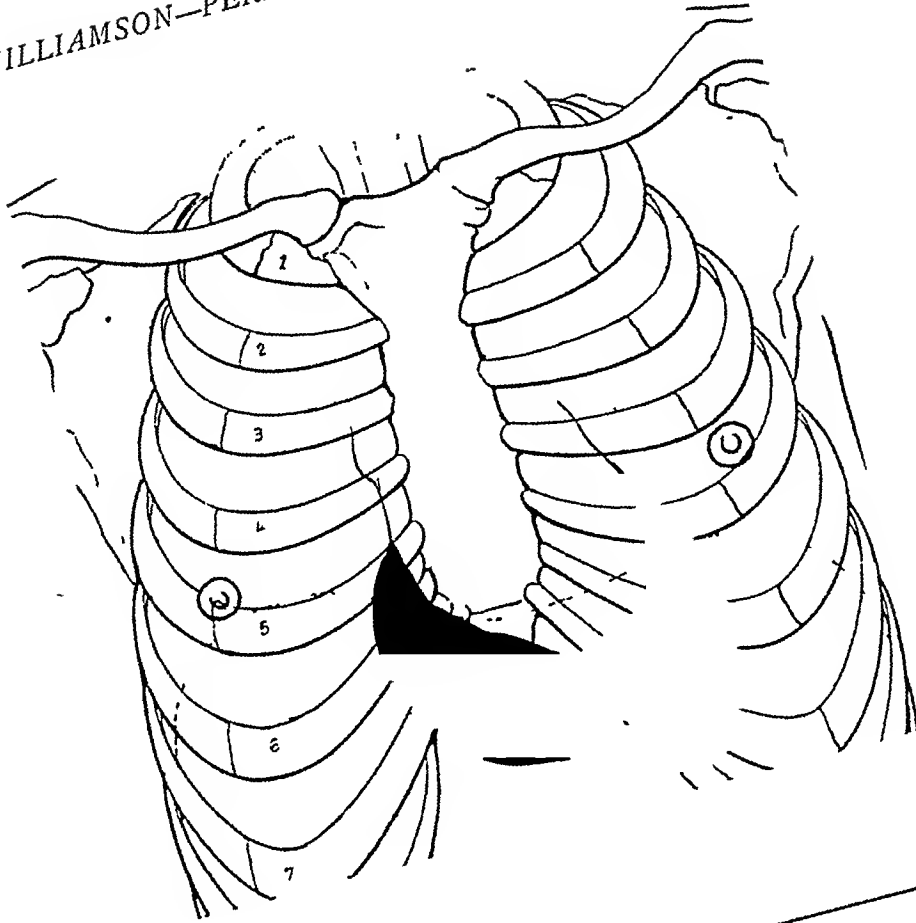


Fig 10—Exp 25, 605 cc injected The striking feature of this experiment is the great displacement of the diaphragm downward. A moderately thick layer of fluid covers the front of the heart and the great vessels (See note, page 206)



of the sternum Right border obscured by the lung dullness Loud to and fro friction rub over the anterior surface of the heart Liver dullness extends two inches below the costal arch " It should be noted that this position of the liver was about an inch below what it had been on admission A study of the photographs and section showed the heart to be surrounded with a fairly uniform layer of fluid, which, however, is somewhat thicker along the left border of the heart, and extends well up over the great vessels at the base This fact we had been able to make out clinically Because of the consolidation in the right lung, we could not determine with accuracy what the condition was at the cardiohepatic angle, but an inspection of the section shows that the amount of exudate there was much too small to be determined by percussion, and that the cardiohepatic angle was certainly not obtuse I wish to lay especial stress on the pushing down of the liver, since it was on this sign, and on the retrosternal dullness that I based my diagnosis of an effusion It should be noted especially *that despite a layer of fluid perhaps one quarter of an inch thick in front of the heart, a pericardial friction rub over this entire area could be heard plainly*

It may be said then, that the principal difference between small and medium sized exudates is that in the latter, in addition to the pushing down of the liver, the heart is more evenly surrounded by fluid It is especially to be noted that the great vessels at the base are covered with a rather thick layer of fluid in the larger effusions of this group This can be seen on almost any of the sections cut longitudinally In most of the cases in which the great vessels were covered by a thick layer of fluid, this could be made out by percussion, but not in all of them, so that while this percussion dullness is to be regarded as a valuable sign when present, it cannot always be made out

From the standpoint of the persistence of the pericardial rub, it is desirable to note in just what cases the heart remained in actual contact with the chest wall This was the case in fourteen of the thirty-three cases In these fourteen cases, exudates of less than 400 cc were found in seven, and exudates larger than this were found in the remaining seven In these fourteen cases, therefore, it is perfectly certain that a pericardial friction rub would have been heard despite the fluid, and recalling the clinical case above enumerated, where a loud friction rub was heard over the entire heart a few minutes before death, although the necropsy disclosed a quarter of an inch of fluid between the heart and the chest wall, it is highly probable that a much larger number would have shown a friction rub despite a fair sized effusion

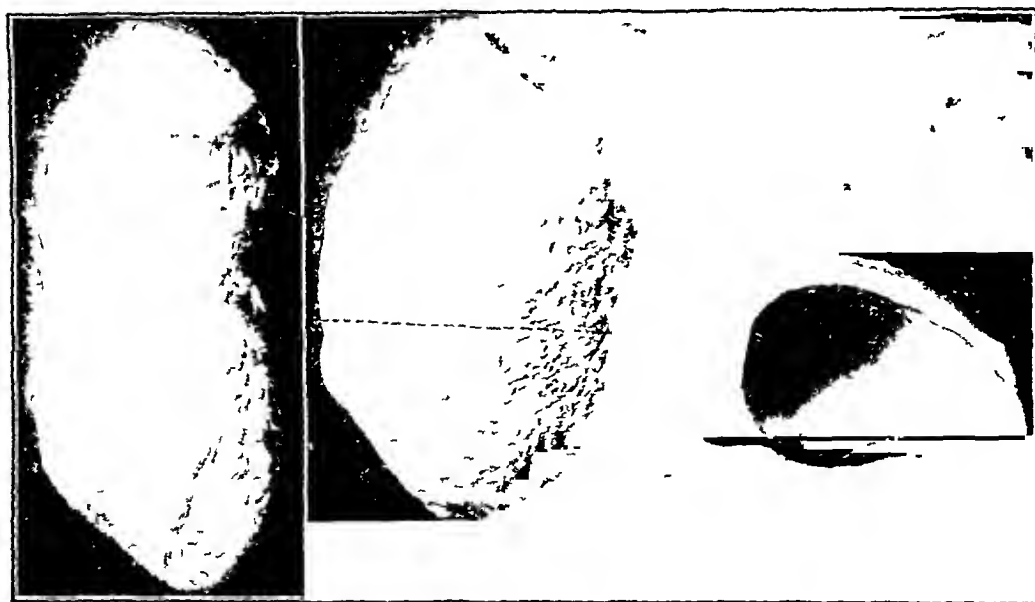
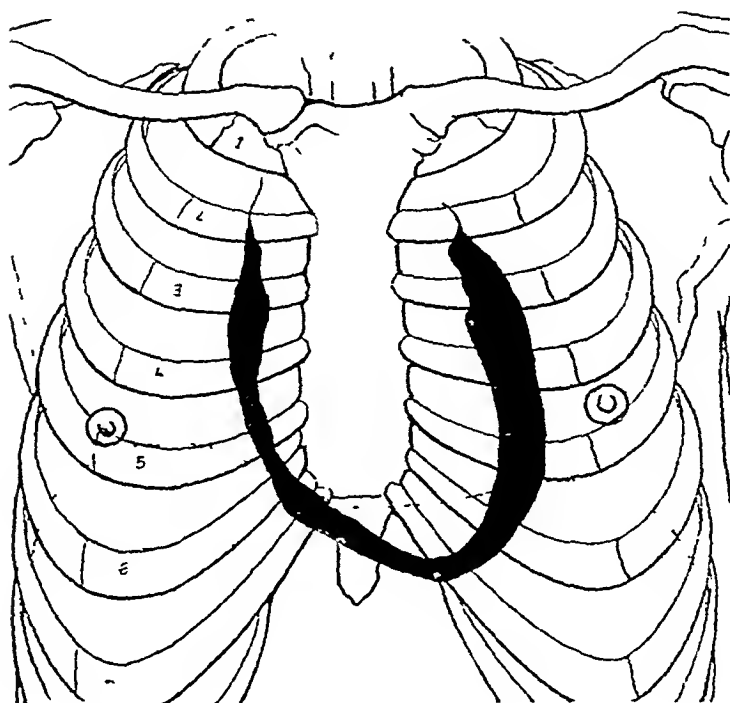


Fig 11—Exp 27, 405 c.c. injected. This was an actual case of pericarditis. The fluid was drawn off immediately after death and replaced by the same amount of agar solution. In this case the exudate surrounds the heart quite uniformly, a little more along the left border. The great vessels are covered by a fairly thick layer of fluid. (See note, page 206.)

*Relation of Size of Heart and Depth of Thorax to Shape of Effusion*—It would not be profitable to give all of the numerous measurements taken as to depth of thorax, circumference of thorax, size and weight of heart, etc. Suffice it to say that I have not been able to make out any simple relationship, capable of being expressed in figures, as to the factors which cause the exudate to spare the front of the heart. Despite my inability to express this numerically, a careful inspection of the cadavers at necropsy showed that whenever the size of the heart was sufficient to fill out very fully the anteroposterior diameter of the thorax, there would be no accumulation in front of the heart. Experiments 1 and 19 (Figs 6 and 9) illustrate this point, Experiment 12 (Fig 7) is a striking example of it. In this individual the heart was very large, weighing 550 gm., and yet the entire front of the heart was bare of exudate, although this contained the largest exudate of the fourteen mentioned above, namely, 475 c c. One may generalize, I believe, with safety, to this extent, and say that when the heart is relatively large, as in valvular lesions with dilatation and hypertrophy, or in cases of chronic nephritis, any exudate which may develop is likely to leave the front of the heart bare, even when the amount of fluid is quite considerable.

#### CONCLUSIONS

1 In pericardial effusion the fluid accumulates first along the lower margin of the heart and about the apex, particularly on the diaphragmatic surface of the heart. With small effusions, this is the only place in which fluid accumulates with regularity.

2 The result of the accumulation of the fluid in this position is to push down the left lobe of the liver. This was demonstrable in practically every case, and in many cases it was a very conspicuous feature. Special stress should be laid on this as an early diagnostic sign.

3 The second place in which fluid accumulates is over the great vessels at the base. With small effusions it is occasionally present in sufficient amount to be detected by percussion. With medium sized effusions this layer is generally thick enough to be demonstrable by percussion, and this retrosternal dullness is an important diagnostic sign.

4 With both small and medium sized exudates we were neither able satisfactorily to demonstrate percussion dullness in the fifth right interspace (Rotch), nor could a rounding of the cardiohepatic (Ebstein) angle be made out in a single case.

5 The behavior of the fluid is practically independent of the position of the patient, with effusions of the size represented by the injections.

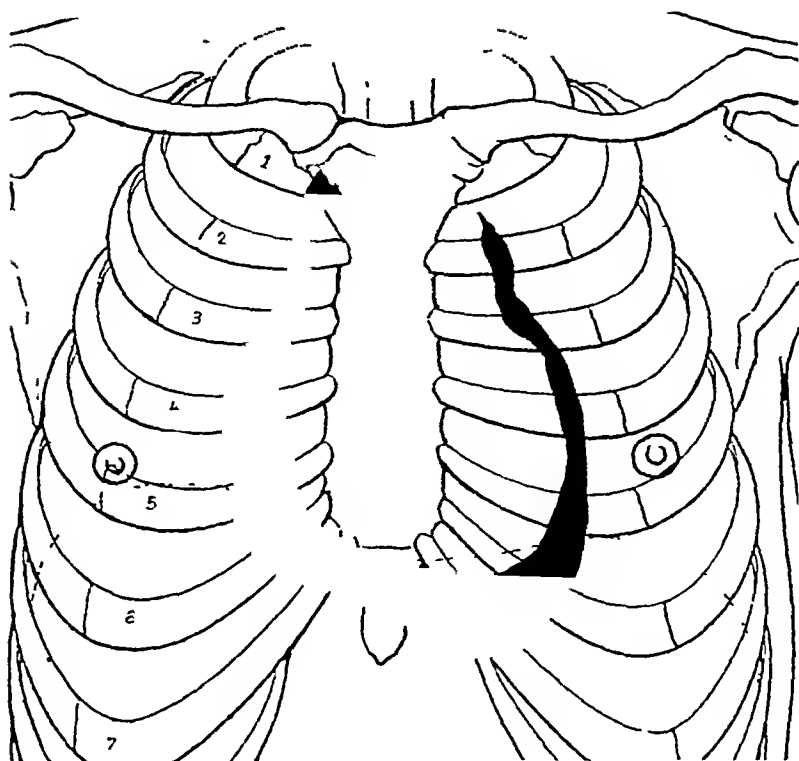


Fig 12—Exp 28, 655 cc injected The larger portion of the fluid is on the diaphragmatic surface and over the great vessels (See note, page 206 )

6 In at least fourteen of the thirty-three cases the anterior surface of the heart, in spite of the exudate, remained, in part, uncovered by the fluid, so that a pericardial friction rub could readily exist. This persistence of the pericardial rub is to be anticipated in cases in which the heart is relatively large, so that it fills out the space between the vertebral column and the sternum.

7 From the standpoint of most readily reaching small amounts of fluid, the most appropriate sites for puncture are either just outside the apex or in the chondroxyphoid angle.

## BOOK REVIEWS

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**SYPHILIS AND PUBLIC HEALTH** By Edward B. Vedder, A.M., M.D., Lieutenant-Colonel, M.C., U.S. Army. Published by permission of the Surgeon-General of the U.S. Army. Cloth, \$2.25, pp. 315. Philadelphia and New York: Lea & Febiger, 1918.

Syphilis is one of the most important public health problems and now that the barrier of reticence is breaking down, a serious effort is being made to spread information about the disease and to take counsel openly in the search for methods that will likely diminish its astonishing prevalence. Even physicians who daily in practice see the fatal consequences of this wide-spread and tenacious infection are scarcely prepared to receive without surprise the actual data on the incidence of the disease and the morbidity and mortality it causes. The time has come when public interest will demand of physicians a knowledge of the fundamental facts about syphilitic infection and the physician must be prepared to answer the demand either of individual persons or of community groups eager to help curtail this public evil. It is very convenient to have these fundamental facts so painstakingly and so clearly assembled as they are in Dr. Vedder's small book. He has gone to original sources for his information and each chapter is followed by a valuable list of references. The prevalence of syphilis, sources of infection and methods of transmission, personal prophylaxis, and public health measures are all satisfactorily considered. A very sane and reasonable attitude is maintained throughout the book, noticeable particularly in his discussion of bitterly contested points, as for instance the propriety of advocating and disseminating information on methods of venereal prophylaxis. The book is written clearly and in simple language so that an intelligent layman may easily understand it. It might with profit be recommended to medical students.

**NEOPLASTIC DISEASES** By James Ewing, A.M., M.D., Sc.D., Professor of Pathology at Cornell University Medical College, New York City. Cloth. Price, \$10.00. Pp. 1027, with 479 illustrations. Philadelphia and London: W.B. Saunders Company, 1919.

Dr. Ewing describes the purpose of his book in the preface. "He has endeavored to analyze the numerous etiologic factors which meet in such diverse fashions in the inception of tumors, to emphasize the general dependence of clinical course upon histologic structure, to trace the histogenesis to the last degree, impressing its essential importance when known, and to enumerate and contrast the more striking clinical features which are often highly characteristic of different tumors. After a brief section dealing with the general principles of oncology the author discusses the different types of tumor and then the varying manifestations of tumors in different regions. Growths are considered regionally rather than histogenetically, a plan that adds greatly to the value of the book from the physician's point of view. Under each organ the different types of tumors that affect it are discussed, the varieties, the etiology, the pathological anatomy, the prognosis and the symptoms. The reviewer has found the book very valuable to himself and recommends it heartily. A great mass of information has been carefully gathered and arranged in easily accessible form. The book is filled with good illustrations, and a carefully selected bibliography serves as a guide to more detailed information upon each topic.

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## STUDIES ON ARTHRITIS IN THE ARMY, BASED ON FOUR HUNDRED CASES

### I PREAMBLE AND STATISTICAL ANALYSIS

RALPH PEMBERTON, M D, Major, M C, U S Army

WITH THE ASSISTANCE OF

J W ROBERTSON, M D, First Lieutenant, M C, U S Army

PHILADELPHIA

The decision of the surgeon general to make special provision for the care and study of chronic arthritis in the Army, has permitted activities in this connection on a scale larger than has been possible in this country since the Civil War, or than seems likely to be possible again. The advisability of such provision was indicated by several factors. Statistics available through the courtesy of Col A G Love, of the Sick and Wounded Division, U S Army, Washington, D C, based on data available up to Jan 1, 1918, indicated that for an army of four million men, for one year, there could be expected an incidence of upward of thirty thousand cases of chronic arthritis, excluding those of a tuberculous or a Neisserian nature. The very limited degree to which our troops had participated in active warfare at the time of compiling the above data suggested that with the subjection of more men to the same conditions these figures would be increased.

Observations by students of this subject among the Allied armies, and an independent survey of the cases presenting at a number of army hospitals in this country, gave added weight to these figures, not only in respect of the numbers, but also in respect of the types and severity of the cases encountered. It was plain, therefore, that chronic arthritis formed one of the larger medical problems affecting the soldier in service, and, hence, the efficiency of the army as a whole.

The marked chronicity of this disease, as compared with most outstanding medical conditions in the army, gives added importance to this fact. Further, the problem of the chronically arthritic soldier is extended to the civil community after his discharge in a degree which bears comparison with that of gunshot wounds. Finally, the incidence of chronic arthritis in civil life and the difficulty of meeting it are



already such as to make desirable efforts to prevent their increase and to justify any well considered action which seeks to utilize the large opportunities created by the war in the study of this disease

Because of the fact that U S Army General Hospital No 9, Lakewood, N J, had already been designated as a center for investigative work, that it had a location easily accessible to returned overseas patients, and because of the presumably advantageous nature of the climate and soil there, the present studies were undertaken at this hospital<sup>1</sup>

The lines of investigation followed were determined by several factors Chief among these were the desirability of studying the metabolism of arthritis as a whole in a larger way than had yet been attempted by modern methods, the previous experiences of one of us (R P), which permitted a point of attack different from most lines of investigation, and the desirability of amplifying these experiences

Most of the recent work undertaken on arthritis has proceeded from a bacteriologic basis, and this phase of the problem has been covered so thoroughly that it appeared improbable that much would be achieved in this direction without extraordinary effort, especially as the investigative personnel and equipment of the hospital were established along physicochemical lines Bacteriologic studies in relation to chemical pathology were suggested, however, by the experience gained, and it is clear in retrospect that bacteriologic work of the nature indicated, would have been of interest

The present report, therefore, considers the following (a) the incidence of chronic arthritis in the army as a whole and a statistical analysis of the factors governing this incidence, the types of cases resulting and such clinical matters as have been suggested in the course of this study, (b) laboratory and clinical studies along a variety of lines, as to the nature of arthritis, based on a large number of the 400 cases presenting, (c) experiences with certain types of treatment, and a brief analysis of some other forms of therapy with their indications, (d) recommendations directed toward lowering the incidence of arthritis in the army, toward the provision of personnel, equipment and other facilities suggested by these studies as important, toward reduction of hospital days and toward the early return to duty of soldiers the subject of this disease

This report does not aim to present the subject of arthritis in the form of a treatise It attempts to reflect the conditions encountered,

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1 The arthritic service was inaugurated at U S Army General Hospital No 9, Nov 16, 1918, and terminated with the closing of the hospital about June 1, 1919, although the admission of patients had ceased and the discharge of patients was completed about two weeks earlier

to describe the work undertaken and to state such conclusions and recommendations as seemed warranted.

### STATISTICS

Under average conditions, chronic arthritis has its highest incidence around the fourth and fifth decades, although it may occur at any age. The factors operating to produce it in young soldiers, under stress of warfare, presumably differ somewhat from those operating in civil life. It was conceivable that such differences might be reflected in a critical analysis of the cases presenting, and that other fact obtainable, such as the distribution of involvement, etc., would also be of interest. The study of each case began, therefore, with a critical and detailed examination as regards a considerable number of factors relating to the date and manner of the onset of the present attack, of the previous attacks, if any, the condition of health prior to the present attack, treatment received, and the like. A complete medical examination followed, including routine, full and differential blood counts, Wassermann test, etc., after which the subject was referred routinely for examination to the eye, ear, nose and throat department, the dental and genito-urinary departments and, when indicated, to the roentgen-ray department. Details regarding these examinations and the actions and conclusions based on them appear under the appropriate headings. Many of the patients were additionally made the subject of particular laboratory and other studies. Most of the patients in the present series were returned from overseas, although a considerable percentage came from camps in this country. More than 420 patients were admitted to or examined by the arthritic service, but the following statistics are based on 400 cases, after eliminating those of doubtful nature.

#### STATISTICAL ANALYSIS OF FOUR HUNDRED CASES OF ARTHRITIS ADMITTED TO U S ARMY GENERAL HOSPITAL NO 9, LAKEWOOD, N. J.<sup>2</sup>

It was found that 256 patients (64 per cent) had arthritis only, 112 (28 per cent) had a combination of arthritis and myositis; twenty-two (5½ per cent) had myositis only, seven (1.75 per cent) had nerve involvement (neuritis) only, and three (0.75 per cent) were listed as doubtful.

The average age of all patients was 28.26 years, while that of the worst cases showing the least improvement was 29.38 years.

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<sup>2</sup> Compiled with the assistance of First Lieut John W. Robertson, M. C. Associated at various times with the arthritis service at this hospital were also Capt Louis A. Levison, M. C., on whom fell much of the routine medical care of the patients, First Lieut Willard Phippard, M. C., and First Lieut Jacob Mitchell, M. C. It is a pleasure to acknowledge the cooperation of these officers, particularly Captain Levison.

The precipitating factors in order of frequency were as follows

	No Cases	Per Cent
Exposure	232	58
Dysentery	33	8.25
Injury	30	7.5
"Flu"	28	7
"Gas"	23	5.75
Drilling and hiking	15	3.75
Tonsillitis	13	3.25
Pneumonia	6	1.5
Neisserian infection	4	1

Under a miscellaneous listing of precipitating factors

- 1 case followed meningitis
- 2 cases followed appendicitis
- 2 cases followed measles
- 3 cases followed mumps
- 2 cases followed scarlet fever
- 1 case followed the injection of pneumococcic vaccine
- 1 case followed acute bronchitis
- 2 cases followed "boils"
- 2 cases followed abscess of the jaw (from tooth)

It was found that in forty-eight cases (12 per cent) there was more than one precipitating factor, for instance, exposure and dysentery may have played an equally important rôle in one and the same case

Fifty-six cases (14 per cent) were listed as having an unknown precipitating factor

One hundred and forty-three patients (35.75 per cent) had had attacks of "rheumatism" prior to their army service. In contrast to this only eight of 113 nonarthritic patients (7 per cent plus) on the surgical and orthopedic wards, questioned at random as to any history of "rheumatism," had had attacks of this nature. In other words, the incidence of previous attacks of arthritis or "rheumatism" was five times more frequent in the cases in this series than in cases at large admitted to the hospital for other conditions. This point is referred to more fully under the caption "Summary."

Statistics compiled under the direction of Capt. Bernard Smith, chief of the cardiovascular department of the hospital, and made available through his courtesy showed that in 350 cases of functional cardiac disorder, the incidence of rheumatic attacks prior to admission to the hospital was less than 6 per cent.

## DISTRIBUTION OF INVOLVEMENT

	No Cases	Per Cent
Knee	248	62
Ankle	141	35 25
Hip	135	33 75
Shoulder	127	31 75
Legs (muscle)	89	22 25
Hand	58	14 50
Spine	54	13 50
Foot	48	12
Wrist	47	11 75
Elbow	39	9 75
Back (muscle)	33	8 25
Arm	30	7 50
Thigh	28	7
Ileosacral joint	16	4
Heel	7	1 75
Sciatic nerve	4	1
Jaw	3	0 75
Lumbosacral joint	2	0 50
Facial nerve	1	0 25

It was noted that 228 cases (57 per cent) showed a combination of two or more of the above distributions, ranging in a few cases up to involvement of practically all joints in the same case

## RELATIVE TO SURGICAL FOCI

The accepted relation of foci of infection to many cases of arthritis made desirable careful analysis of all cases in this regard. Fuller consideration of this analysis follows presentation of the figures resulting

One hundred and seven persons (26 75 per cent) were taken sick in the apparent absence of demonstrable surgical foci. Two hundred and ninety-three persons (73 25 per cent) showed demonstrable surgical foci. Of this latter number 208 showed foci in the tonsils. This is 52 per cent of the entire series and is 71 per cent (minus) of all cases (293) showing foci.

One hundred and thirty-four persons (33 50 per cent) in the entire series, or 45 73 per cent of those showing a demonstrable surgical focus, were positive for a dental focus. Fifty persons, 12 50 per cent in the entire series, or 17 per cent (plus) of those showing a focus, were positive for a genito-urinary focus. Of the above 293 persons showing a focus in any of the above three distributions, seventy-eight (19 50 per cent of 400) showed a combination of both dental and tonsillar foci. This is 26 62 per cent of the 293 persons having a focus somewhere.

It was also found that thirty-eight persons showed some combination of foci other than dental and tonsillar, as for instance dental and genito-urinary or tonsillar and genito-urinary. This number was 9 50 per cent of the entire series or 13 per cent (minus) of the 293 persons showing foci.

## REGARDING PROGRESS

No Cases	Per Cent	Remarks
92	23	Recovered in the apparent absence of a demonstrable focus
184	46	Recovered in the presence of a demonstrable focus
34	8.5	Recovered after the removal of foci
31	7.75	Were improved after the removal of foci
28	7	Were unimproved after the removal of foci
310	77.5	Recovered "by whatever means"
74	18.5	Improved "by whatever means"
16	4	Were unimproved "by whatever means"

On a basis of the last 100 cases of the series, investigated more fully for this point, five patients (5 per cent) improved in the apparent absence of foci, twenty-five (25 per cent) improved in the presence of unremoved foci.

Several points of interest are developed from a study of these figures. Exposure took precedent of all other factors as the exciting agent. There is, of course, in any statistical compilation room for error in the emphasis placed on any one factor, but the clear-cut statements of the soldiers questioned, and the unanimity with which these agreed, made it clear that after making all allowances for error, exposure to cold and wet is a factor of major importance in producing rheumatoid and arthritic disabilities among soldiers in service under present conditions of warfare.

By the term "exposed to cold and wet" is meant protracted subjection to such conditions as deep mud or heavy rain which kept the men, or at least their legs and feet and often their entire bodies, wet for hours, days or even weeks at a stretch. Sleeping consecutive nights on stone or cement floors or wet earth in stone outhouses is also included under this head, and figured frequently not only in the histories elicited, but as causative factors in the conscious experiences of the men themselves. In one extreme example of this series, disability dated abruptly from being caught between allied and enemy fire in a swamp where the command was forced to remain sixty hours, during which time this soldier was in water up to his knees. Other such and repeated instances leave no doubt as to the etiologic relation of exposure of various kinds.

It is of interest that the factor next most frequently encountered after a marked percentage drop was dysentery, which is separated by relatively small differences from injury and "flu." Under "Clinical Considerations," mention will be made of certain points of interest in this connection. It is noteworthy that drilling and hiking were recorded as the exciting factors in only a small percentage of cases, namely, 3.75 per cent.

Analysis of the distribution of involvement indicates that the frequency of disability in the knee is outstanding in contrast to involve-

ment of the ankle, hip and shoulder. This suggests an immediate influence from trauma on the weight bearing parts. The frequency, however, of involvement of the knee under civil conditions, the fact that the shoulders were involved almost as frequently as the hip and ankle, the fact that in a great majority of instances the disease was more or less systemic in its manifestations, and the impressive evidence adduced by the men themselves in relating their disabilities to cold and wet, would seem to indicate that mechanical agencies, such as trauma in marching, played a rôle not conspicuously greater than they do in civil life.<sup>3</sup>

The involvement of the jaw among soldiers was conspicuously infrequent as compared with civil life. The phalangeal and metacarpophalangeal joints of the hand were involved in 14½ per cent.

Certain interesting and instructive relations were indicated by the analysis of all cases presenting in this series for surgical foci in any part of the body. As mentioned, efforts to this end formed one of the fundamental bases of study and treatment of this group.<sup>4</sup> It is generally conceded that the most frequent sites of focal infection are the tonsils, teeth, genito-urinary tract and accessory sinuses of the head, although it may occur almost anywhere in the body. The question of what constitutes pathology, particularly in the tonsils, and when it potentially operates as a focus of infection is a matter on which there is much room for discussion, and it is probable that no observations to this end can be immune from criticism. It is particularly difficult to determine the absence of all foci of infection, and in this connection evidence must be largely presumptive, however carefully obtained. Studies at the hands of many observers, and experience afforded by the work here presented, indicate that harmful foci may be contained within tonsils deeply buried and innocuous in appearance. At the hands of critical observers, however, it is possible to indicate, in a great majority of cases, when present, the existence of definite pathology, particularly perhaps in the teeth, where the roentgen rays often confirm or refute suspicious evidence. It is probable, therefore, that the error on the positive site is small.

Referring to the figures, it will be noted that 107 patients, or about 27 per cent, were taken sick in the apparent absence of demonstrable surgical foci in the head, nose, throat, teeth or genito-urinary tract.

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3 In a thorough analysis of the results of tonsillectomy in 200 consecutive cases of myositis and arthritis, Lillie and Lyons (*J A M A* 72 1214 [April 26] 1919) found that under civil conditions the knees were involved with greater frequency than other joints.

4 Obligation is expressed for the painstaking and cooperative efforts of the medical officers conducting the department of the eye, ear, nose and throat, especially Capt Watson W Garley, Jr, and Capt T W Davis, M C, U S Army.

Bearing in mind that there is a possible error in the exact number classed in this category, it nevertheless becomes apparent that an important percentage of these soldiers were free from the gross pathology so frequently found in civil life in connection with this disease. On the other hand, 184 patients, or 46 per cent, recovered in the presence of demonstrable foci. This fact is particularly instructive. It is less impressive when indicated by figures than when demonstrated by intimate contact with scores of men, invalided for months, and, in many cases, a year or more by severe and widespread arthritis, who have achieved recovery without residual pathology along lines of expectant treatment, aided sometimes by local measures. Under the pressure of war conditions, it was clearly difficult or impossible to give these men the attention they deserved and should have had. In view of the large rôle played by exposure as an exciting factor, in view of the recovery from arthritis of many soldiers carrying demonstrable surgical foci, usually in their tonsils, it is impossible to escape the conclusion that the men constituting the group here studied, showed a large independence of focal infection. It is to be borne in mind that many men were convalescing or well on admission to the hospital. Many men would certainly have gotten well sooner had their foci been removed. It should not be deduced that the removal of foci is unimportant. It is of great importance and is made the basis of one of the recommendations to be mentioned later. In this particular group, however, it must be recognized that more men got well with no attention to foci than got well after removal of them. This conclusion will appear somewhat at variance with the relation focal infections are known frequently to bear to the disease, and should not be interpreted as justifying neglect of this established rôle, indeed, the evidence adduced from this series substantiates this relation strongly. Bearing this relation in mind, however, it is proper, if possible, to establish its limits etiologically and therapeutically. It is probable that there is here evidenced a distinct contrast to the conditions influencing chronic arthritis in civil life, and that the age of the subjects and the recuperative powers of youth must be given large significance. Under "Treatment," mention will be made of the possible practical application of this conclusion.

It is of much interest to note that only fifty cases, or 12½ per cent, of the series showed a possible focus in the genito-urinary tract. Indeed, of this number showing demonstrable pathology, only a trifling number were believed to have actual relation to the intercurrent arthritis, and it seems safe to conclude that genito-urinary infections played a small rôle in the causation of chronic arthritis in the army. The focal genito-urinary infections found were referable in only a

small percentage to venereal disease per se<sup>5</sup> It is also of interest to note that only eight cases, or 2 per cent, showed a sustained and undoubted Wassermann reaction This entirely corroborates the experience of one of us (R P) in civil life, and there seems little doubt that syphilis plays a negligible rôle in the causation of chronic arthritis

#### DENTAL FOCI

An analysis of 397 cases for the percentage incidence of the various types of dental pathology was prepared by Capt W E Mentzer, Dental Corps, to whom obligation must be expressed for cordial and skilful cooperation<sup>6</sup> As noted above, definite dental foci of infection presented in only 134 cases, or 33½ per cent, and tonsillar foci were present in 208 cases, or 52 per cent It is rather astonishing that the combination of tonsillar and dental pathology should be present in only seventy-eight, or 19½ per cent of the entire 400 cases This was not due to over-attention to one focus, when found, with consequent neglect of other possible foci, as all cases were examined routinely and independently

In examining patients from the dental standpoint, any condition about the mouth from which absorption might take place, was considered a possible focus, and the case was studied further from that standpoint The subject of caries was divided into three classes, respectively, slight, medium and heavy, to assist the dental department in giving attention first to the most needy cases Under "caries slight" are classed the cases in which the enamel was etched or just broken, under "caries medium," are classed the cases in which the decay had proceeded farther, but not far enough to endanger the pulp, and under "caries heavy," are classed the cases in which the pulp was endangered or already exposed

Conditions falling under the classifications "simple gingivitis," and "condition of the gums, fair or poor," were not regarded as foci, but were considered as paving the way for infection and suppuration, and were corrected immediately to prevent the deeper tissues from becoming involved The number of cases falling under "gingivitis simple," and "condition of gums poor," was large owing to the fact that these patients were not able to give their mouths the average amount of care This is illustrated by the number of subjects showing salivary deposits Under "pockets" about the necks of teeth have been listed all cases where such conditions were found, whether suppurative or

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<sup>5</sup> Opinion of Capt George G Smith, chief of the genito-urinary service at U S Army General Hospital No 9

<sup>6</sup> All 400 cases were analyzed for dental foci as mentioned, but calculation of the percentage incidence of different kinds of dental pathology was made on only 397 cases



nonsuppurative Very few of these cases were suppurative, the larger number, being caused by calculus deposits or the impaction of food between the teeth, had not progressed to that degree When ulcerative gingivitis was present, or when there were pockets about the necks of the teeth, it became necessary for the examiner to determine whether in his opinion the condition present constituted a focus or not

Under abscessed teeth come the various alveolar abscesses, acute, chronic (with and without sinus) and blind abscesses, all of which were classed as constituting foci The roentgen rays were resorted to when there were deep pockets about the necks of the teeth and in all cases in which there was the least possibility of an apical abscess An analysis of 397 cases revealed the following conditions in the proportions indicated

Caries, slight	118, not constituting a focus
Caries, medium	80, not constituting a focus
Caries, heavy	79, not constituting a focus
Calculus, subgingival	211, not constituting a focus
Calculus, salivary	116, not constituting a focus
Condition of gums, good	164, not constituting a focus
Condition of gums, fair	103, not constituting a focus
Condition of gums, poor	112, not constituting a focus
Gingivitis, simple	216, not constituting a focus
Gingivitis, ulcerative,	25, constituting a possible focus,
Pockets about necks of teeth,	77, constituting possible foci,
Abscessed teeth,	126, constituting foci of infection,
Incidence of abscessed teeth among all cases examined, 30 per cent	

Only nine cases showing either pockets about the necks of the teeth or ulcerative gingivitis, or both, were considered actual foci of infection, making a total of 135 instances, or 34 per cent

# STUDIES ON ARTHRITIS IN THE ARMY BASED ON FOUR HUNDRED CASES

## II OBSERVATIONS ON THE BASAL METABOLISM

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Few, if any, observations have been available to date on the basal metabolism of chronic arthritis. Some of the evidence regarding this disease has indicated that a variety of agents whose action is supposed to hasten the body metabolism, such as thyroid extract, radium and the roentgen ray, may, at times, exercise definitely beneficial effects, and that certain subjects of chronic arthritis do very much better on a lowered food intake, particularly of carbohydrate, than they do on an unrestricted diet<sup>1</sup>. These, and other, considerations have suggested that there might be in chronic arthritis a lowering or retardation of the body metabolism which would express itself in summation figures, although it is, of course, possible that the intermediary metabolism might be markedly disturbed without being reflected in such totals. The basal metabolism was, therefore, studied in a series of twenty-nine cases. The observations were made by indirect calorimetry, using the Tissot method. Analyses of the expired air were carried out on the Haldane gas apparatus<sup>2</sup>. Table 1 shows the results obtained. Of the twenty-nine cases studied, 80 per cent showed a metabolism within normal limits, 20 per cent showed a metabolism slightly below normal limits<sup>3</sup>. The metabolic data give no explanation for this deviation. From the respiratory quotients no abnormality can be detected in the percentage of calories obtained from the three foodstuffs. Nothing abnormal was found in the pulse, temperature or minute volumes of air breathed at the times of the determinations. In the cases showing a basal metabolism below the normal limits, no particular relation could be determined between the severity of the disease, age or condition of the patient (whether active or bed-ridden), atrophy of muscle, edema or other factors.

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1 Pemberton, R. *Am J M Sc* **153** 678 (May) 1917

2 Peabody, Wearn and Tompkins. *The Basal Metabolism in Cases of the Irritable Heart of Soldiers*, *Med Clin N America* **2** 507 (Sept) 1918

3 The second experiment on Robbins is not included in either percentage because he was then on a limited diet

TABLE 1—BASAL METABOLISM IN TWENTY-NINE CASES OF CHRONIC ARTHRITIS

Name	Case	Date	Age	Height, Cm	Weight, Kg	Rectal Temperature F	Pulse	C c of CO <sub>2</sub> per Minute	C c O <sub>2</sub> per Minute	Respiratory Quotient	Volume per Minute, L	Calories per Sq Meter	Metabolism Percentage from Normal
Masood	10	11/21	23	167	57.7	98.8	75	186	226	0.83	5.13	39.8	-1
Grondyke	83	1/21	59	160	50.0	98.4	85	150	176	0.85	4.66	34.2	-2*
Brice	16	1/16	46	173	53.9	98.2	78	168	212	0.79	4.28	37.3	-3
Dekim	84	9/21	42	174	64.3	98.4	64	171	235	0.73	4.67	37.6	-3†
Leeman	85	9/22	19	174	58.2	97.8	67	219	227	0.97	6.55	40.0	-3
Hinman	11	12/13	25	161	57.0	97.5	52	181	206	0.88	4.91	38.1	-4
Stone	28	1/6	40	167	53.9	97.7	59	186	194	0.96	5.06	36.5	-5*
Cox	79	12/7	36	177	65.9	97.4	59	191	236	0.81	6.04	37.4	-6
Jaffy	7	11/22	24	168	50.7	98.2	73	156	203	0.77	4.70	37.1	-6
Hayes	6	12/7	29	180	56.6	97.7	68	167	218	0.77	4.51	36.2	-8
Robbins	1	11/19	25	192	78.4	98.7	69	229	257	0.89	5.90	36.6	-8
Robbins	1	1/6			77.3	97.6	61	184	245	0.75	4.86	34.2	-14
Lumers	13	1/9	40	163	47.3	97.0	67	134	169	0.79	3.83	32.8	-19
Beck	5	11/19	26	189	65.0	97.4	55	199	232	0.86	4.82	35.9	-10
Lowe	14	1/28	42	177	60.1	97.6	60	184	216	0.86	5.50	34.1	-11
Zuch	86	12/6	25	172	70.5	98.0	54	167	226	0.74	4.00	35.0	-12
Sharpe	87	12/4	46	178	78.4	97.8	62	191	229	0.84	4.64	33.8	-13
Haeberle	2	12/7	29	175	68.4	97.6	73	158	216	0.73	3.91	33.4	-15*
Blowers	3	12/2	41	179	68.2	97.7	58	160	211	0.80	4.89	32.7	-16
Martin	8	11/20	45	172	66.6	98.2	72	139	191	0.73	5.01	30.6	-21
Oberg	22	2/3	24	169	49.7	98.4	93	168	214	0.79	4.42	39.6	+0
Bartholomew	88	12/10	26	178	81.8	97.4	65	223	277	0.81	6.24	40.0	+1
Cichon	89	12/9	22	163	61.6	98.1	59	188	229	0.83	5.99	39.9	+1*
Mulledy	90	11/21	21	178	78.3	98.4	66	220	279	0.79	5.99	40.7	+3*
Saxton	91	9/22	24	181	71.6	98.0	65	207	270	0.77	6.64	40.5	+3
Kolden	92	9/21	28	171	60.7	98.0	72	205	251	0.82	5.71	42.2	+7†
Hamburg	93	12/9	23	168	62.0	98.4	76	200	260	0.77	5.13	43.1	+9
Meadows	94	11/21	23	168	52.5	97.8	52	200	235	0.85	6.52	43.1	+9§
Boyd	12	12/13	24	165	49.5	98.5	80	199	228	0.87	5.45	43.7	+11

\* Periods disagreed by 4 per cent

† Periods disagreed by 5 per cent

‡ Periods disagreed by 6 per cent

§ Restless in Period II, periods disagreed by 8 per cent

# STUDIES ON ARTHRITIS IN THE ARMY BASED ON FOUR HUNDRED CASES

## III STUDIES ON THE NITROGEN, UREA, CARBON DIOXID COMBINING POWER, CALCIUM, TOTAL FAT AND CHOLESTEROL OF THE FAST- ING BLOOD, RENAL FUNCTION, BLOOD SUGAR AND SUGAR TOLERANCE

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### NITROGEN AND UREA OF THE BLOOD

In previous communications<sup>1</sup> evidence was advanced to show that there is no disturbance of the fasting level of the blood urea or non-protein nitrogen in cases of chronic arthritis. It was believed important, however, in studying the present relatively large group to include consideration of these factors in order further to substantiate or disprove these findings. Accordingly, determinations of blood nitrogen and urea were conducted in a series of seventeen cases. The blood samples were collected in the morning before the patient received his breakfast. Nonprotein nitrogen was determined by the direct nesslerization method of Folin and Denis<sup>2</sup> and blood urea by the method of Van Slyke and Cullen<sup>3</sup>. The figures herewith appended show that all cases, including those of the most severe type, fall well within normal limits. These observations were further supported by independent determination by Lieut. Thomas E. Buckman, M C, on the blood nitrogen made in connection with studies on creatin and creatinin (see section devoted to this subject) using ten patients of the present series as well as many other patients, a total of fifty. In a series then of sixty-seven observations in fifty-seven cases of chronic arthritis the fasting blood nitrogen fell within normal limits in all but two cases. One of these patients was a man, aged 46 years, with cirrhosis of the liver and renal calculus, who gave 45.4 mg of nitrogen per hundred c c of blood. The other patient was a man, aged 21 years, with a chronic arthritis of one knee, who gave 38.5 mg. There was no other evident disturbance of his health.

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1 Pemberton, R. Am J M Sc **147** 423 (March) 1914

2 Folin and Denis. J Biol Chem **26** 473, 1916

3 Van Slyke and Cullen. J Biol Chem **19** 211, 1914

TABLE 1—BLOOD UREA AND NONPROTEIN NITROGEN \*

Name	Case	Date	Nonprotein Nitrogen, Mg	Urea Nitrogen, Mg
Heaberle	2	1/22	29.7	13.6
Robbins	1	1/9	30.5	14.2
Hayes	6	1/10-2/6	23.5	12.6
Martin	8	12/26	27.5	13.1
Jaffy	7	1/10	28.0	13.4
McGrann	4	1/10	28.2	18.2
Studebaker	15	1/16	29.3	15.0
Boyd	12	1/9	24.6	11.8
Hinman	11	1/6		14.5
Masood	10	12/31		14.0
Lowe	14	1/13	23.5	11.0
Wassoon	20	1/29	30.0	14.0
Whittington	21	1/31	27.8	14.7
Oberg	22	1/31	23.0	11.2
O'Brien	23	2/4	26.8	10.4
Faulkner	17	1/22	22.3	11.0
Mrs K	53	3/29	25.0	11.3

\* For further observations on nitrogen of the fasting blood, see the section on creatin, Part IV

## CARBON DIOXID COMBINING POWER OF THE BLOOD

Studies were conducted in a series of seventeen cases of chronic arthritis in respect of the carbon dioxide combining power of the blood as an index of acidosis. In three of these cases determinations were repeated, making twenty observations in all. In every case the figures fell well within normal limits, the lowest being 53 and the highest 67. The determinations were made on the blood plasma by Van Slyke's gastometric method.<sup>4</sup> Cases 6, 8, 7, 4, 10, 14 and 22 of this series showed advanced disease.

TABLE 2—PLASMA BICARBONATE

Name	Case	Date	CO <sub>2</sub> Volume per Cent	Date	CO <sub>2</sub> Volume per Cent	Remarks
Heaberle	2	1/22	64			Great bone atrophy
Robbins	1	12/30	64			Severe type
Hayes	6	12/26	57			Severe type
Martin	8	12/26	65			Severe type
Beeman	9	12/26	64			Mild type
Jaffy	7	1/10	53	)		Severe type
McGrann	4	1/10	54			Quite severe
Studebaker	15	1/16	64			Quite severe
Boyd	12	1/9	65			Intermittent type
Hinman	11	1/2	60	1/6	62	Mild type
Masood	10	12/31	61	1/2	59	Severe type
Lowe	14	1/13	58			Severe type
Wasson	20	1/29	67			Severe type
Whittington	21	1/31	67			Quite severe
Oberg	22	1/31	59	2/4	67	Severe type
O'Brien	23	2/4	58			Severe type
Faulkner	17	1/22	61			Mild type

4 Van Slyke J Biol Chem 30 397, 1917

## THE CALCIUM OF THE CIRCULATING BLOOD

In view of the known absorption and deposition of lime salts in chronic arthritis affecting the osseous tissues it was thought interesting to include observations on the calcium in the fasting blood in various types. There can be little question that in the processes which result in atrophy or overgrowth of bone there is a disturbance of the normal calcium balance between the fixed and the fluid tissues and possibly of the total body balance as well. Goldthwaite, Painter and Osgood<sup>5</sup> have reported a loss of calcium in the cases of atrophic and hypertrophic arthritis studied by them. It was not practicable, however, to conduct calcium balance determinations in the present series. Clinically, cases and types of arthritis differ markedly in respect of the absorption or deposition of bony tissue and dependable variations of the blood calcium might be of value for differential diagnosis or classification. Observations were accordingly made on the blood calcium under fasting conditions by means of Lyman's nephelometric method.<sup>6</sup> Ten cases were studied and the results obtained were found to fall with surprising uniformity within normal limits corresponding well with other determinations made in the same laboratory on other types of disease and on healthy individuals. The cases studied were mostly of great severity, although three patients of the series represented milder types.

TABLE 3—BLOOD CALCIUM

Name	Case	Date	Calcium, Mg per 100 Cc.	Remarks
Love . . . . .	14	4/8	7.1	Severe
Jaffy . . . . .	7	4/8	7.3	Convalescing
McIntyre . . . . .	69	4/8	7.3	Moderate
Hayes . . . . .	6	4/8	7.2	Severe
Whittington . . . . .	21	4/9	6.5	Moderate
Crawford . . . . .	71	4/9	7.2	Severe
McKenzie . . . . .	62	4/28	7.3	Severe intermittent
Oberg . . . . .	22	4/28	7.2	Severe
Cotter . . . . .	55	5/1	7.3	Mild
Jansen . . . . .	48	7/2	7.1	Improving

## THE TOTAL FAT AND CHOLESTEROL OF THE FASTING BLOOD

A considerable field of investigation has been opened up of late in connection with the blood fats and cholesterol and their relation to metabolism: more particularly since the introduction of Bloor's simpler analytical methods. There has been made possible the accumulation of data in a variety of pathologic conditions tending to place certain

<sup>5</sup> Goldthwaite, Painter and Osgood. *Am. Med.* 7:547-590 (April 2 and 9) 1904.

<sup>6</sup> Lyman: *J. Biol. Chem.* 29:169, 1917.

phases of the metabolism of fat on a basis analogous to that obtaining with the nitrogen and urea of the blood Apart from the desirability, on general grounds, of utilizing these methods in studying the metab-

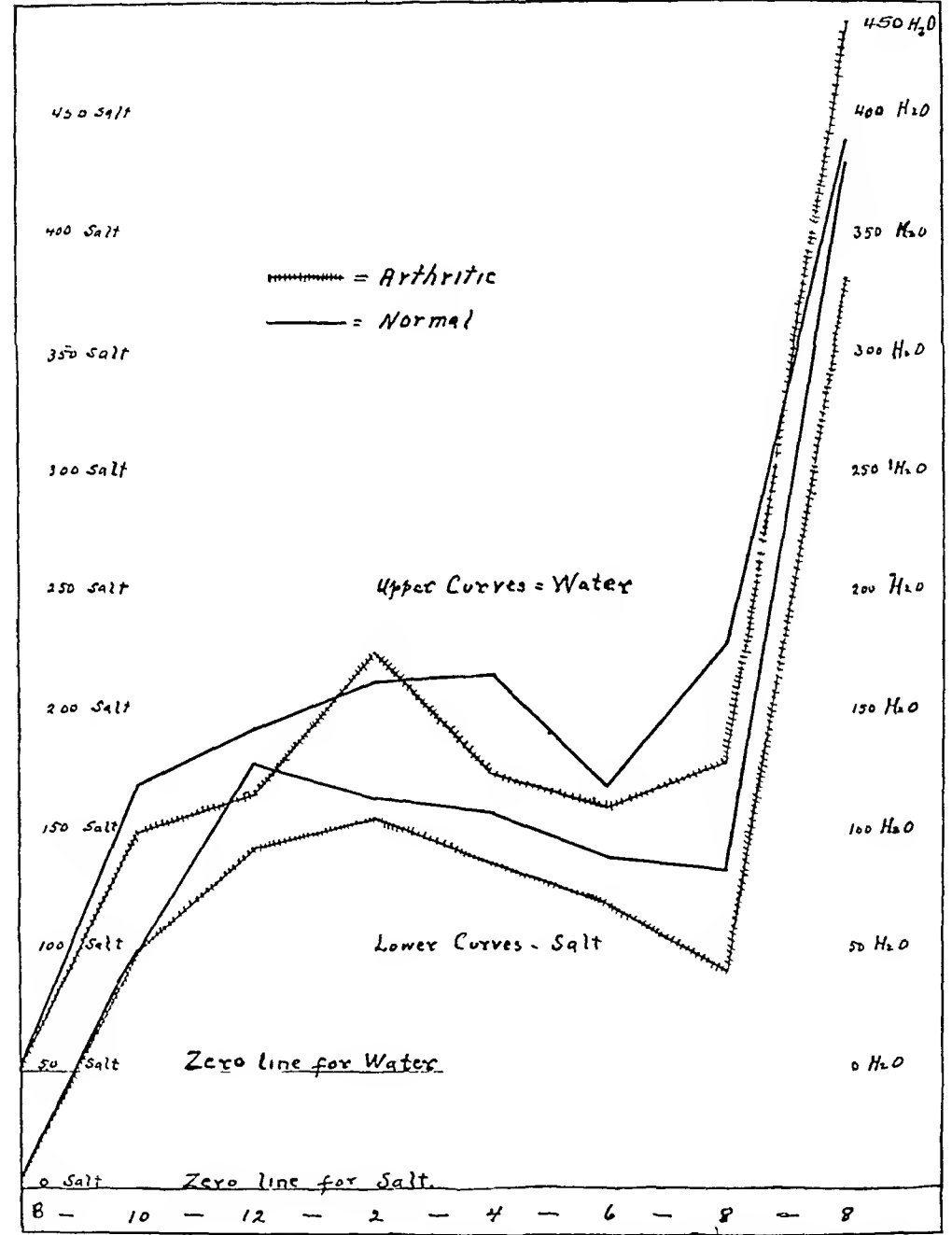


Chart 1—The salt and water output for normal persons and arthritis patients

olism of arthritis, such considerations were given added relevance by the evidence at hand regarding blood nitrogen, blood sugar and the influence of a reduced diet in this disease (see sections devoted to these topics) Studies were, therefore, conducted on the total fats

and cholesterol of the fasting blood, using the method of Bloor.<sup>7</sup> Determinations were made on fourteen subjects, but gave, as Table 4 shows, results which fall within the rather wide range attributed to normal values. All degrees of severity of the disease were represented

TABLE 4—BLOOD LIPOIDS

Name	Case	Date	Total Fat		Cholesterol	
			Blood, per Cent	Plasma, per Cent	Blood, per Cent	Plasma, per Cent
Robbins	1	1/19	0.668	0.738	0.165	0.137
Hayes	6	1/10	0.616	0.680	0.093	0.082
Jaffy	7	1/10	0.381	0.465	0.079	0.072
McGrann	4	1/10	0.400	0.410	0.080	0.075
Boyd	12	1/9	0.630	0.690	0.144	0.109
Hinman	11	1/6	0.420	0.600	0.078	0.077
Masood	10	1/6	0.360	0.483	0.124	0.101
Lowe	14	1/13	0.416	0.440	0.103	0.097
Wasson	20	1/29	0.410	0.460	0.097	0.067
Whittington	21	2/4	0.378	0.438	0.098	0.075
Oberg	22	2/4	0.418	0.444	0.073	0.070
Jansen	48	5/5	0.380	0.420	0.086	0.068
Herron	60	5/5	0.415	0.448	0.090	0.071
Cotter	55	5/5	0.432	0.450	0.095	0.070

## THE RENAL FUNCTION

Until the rôle frequently played by focal infections was appreciated, it was long the custom, and still is in many quarters, to attach chief importance to the stimulation of all eliminative functions, particularly those of the skin, as factors in the therapeutics of arthritis. It cannot be denied that there is evidence that such measures play a useful, if limited, rôle, especially in combination with other measures, in cases tending to improve and those in which the basis is laid for convalescence. Their importance per se, however, has possibly been somewhat overestimated. They rarely remove the cause of the disease, and the results attributed to them are sometimes referable to other incidental or intended factors. It is further possible, or even probable, that the measures necessary to promote elimination through the skin depend for their beneficial effect on factors of which the sweating per se is largely an incidental consequence. Efforts at increasing elimination by copious drinking of water, and even by active purgation, have also had large emphasis at many hands, and one patient in the present series had lost 20 pounds in weight from active daily catharsis long continued. The value of compensatory elimination through the skin and bowels in certain nephritic states cannot be doubted, and long ago suggested itself as possibly of value in arthritis. Whether its benefits in arthritis depend on the inability of the kidney to perform its normal functions properly, however, has been the subject of only a limited amount of study.

<sup>7</sup> Bloor J Biol Chem 17 377, 1914, 23.317, 1915



Evidence adduced by one of us<sup>8</sup> (see also chapter on blood nitrogen) as to the renal function in arthritis, when measured by the phenolsulphonephthalein test and the urea and noncoagulable nitrogen of the blood, has indicated no departure from normal as far as these tests are concerned. It seemed advisable, however, to examine the question of renal function from another angle in view of the exceptional number of subjects and their relative freedom from the factors of later life which might cloud the issue.

No attempt will be made here to weigh the values of the various tests of kidney function or their worth in indicating the nature of the underlying pathology. Suffice it, that of the several methods, the

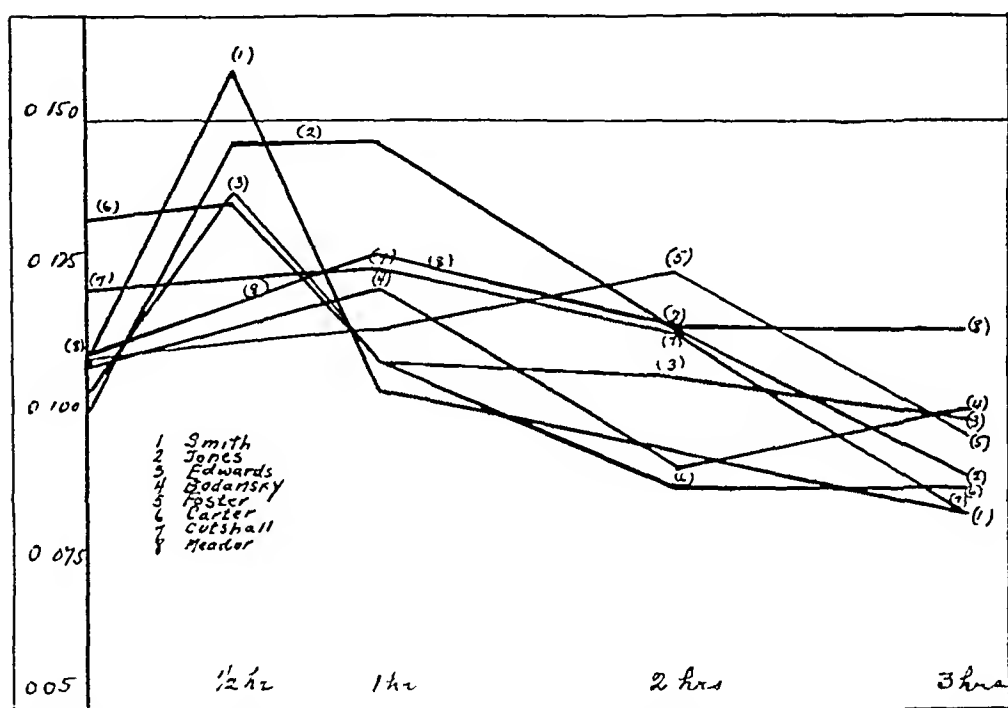


Chart 2—The curves of sugar tolerance in eight normal individuals. The ordinates are percentage concentrations of blood sugar, the abscissae are time periods of one half, one, two and three hours, respectively. The black transverse line in this and the following charts corresponds to a percentage sugar concentration of 0.150 and is at the approximate upper limit of normality after feeding 100 gm of glucose. The glucose was ingested immediately after determination of the first point on each curve. The second point was determined one-half or one hour, generally one-half hour, after the first

method depending on the renal test meal of Hedinger and Schlayer, modified by Mosenthal<sup>9</sup> probably gives the earliest indications of diminished kidney efficiency, and, in addition, has not been applied hitherto to the study of arthritis in any large way. This test depends

<sup>8</sup> Pemberton, R. *Am J M Sc* 147 423 (March) 1914

<sup>9</sup> Mosenthal and Lewis. *J A M A* 67 933, 1916

on the eliminative response of the kidney to approximately constant amounts of water, salt and nitrogen ingested in a generous mixed dietary of about 2,100 calories. We, therefore, adopted this test as a further means of studying the renal function in a considerable series of arthritics and normal individuals, and followed, with a few modifications, the directions laid down by the authors

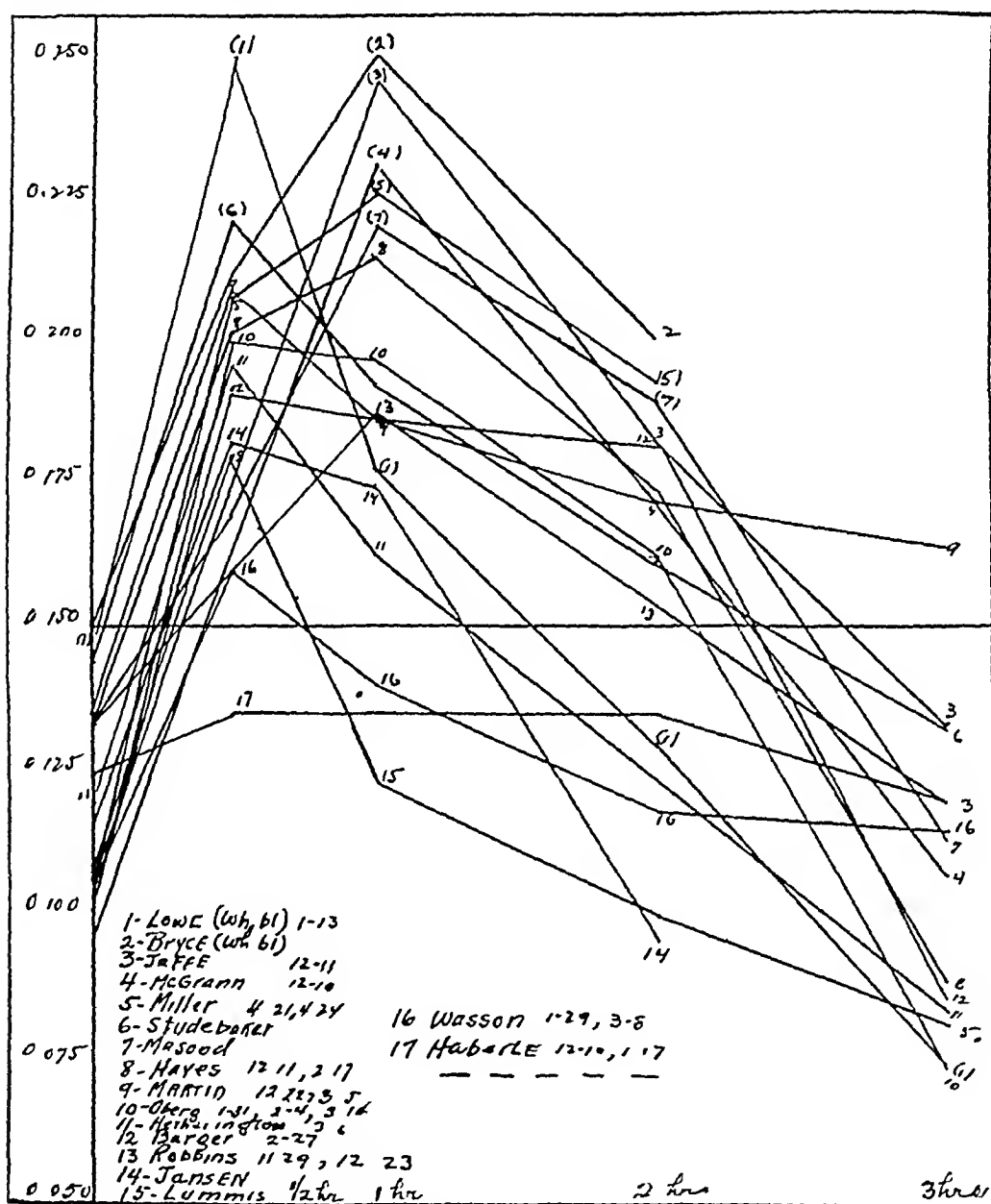


Chart 3—The lowered sugar tolerance in severe arthritis

At 8 a m the patient emptied the bladder and was then given breakfast, the urine was then collected in two-hour periods up to 8 p m. The midday and evening meals were taken at 12 noon and 6 p m, respectively. The night urine from 8 p m to 8 a m was collected in one specimen. The urine was examined in the usual way

for volume, specific gravity and chlorids, and the total nitrogen was determined on the composite twenty-four-hour amount

During the day of the test the patient was required to keep as quiet as possible, and all medication and physiotherapy which might vitiate the results were omitted. The patient was watched carefully, and results were discarded when there was suspicion that the patient did not follow directions closely. The diet administered was prepared by trained dietitians in the diet kitchen<sup>9a</sup>. Its composition is indicated in Table 5. It corresponds to the so-called "high" protein diet used by Mosenthal, although he has indicated that certain characteristics, as shown "by the specific gravity of all the specimens and the volume of the night urine, are present regardless of the diet and may be regarded as the normal standards by which to judge similar tests in abnormal individuals"<sup>10</sup>.

TABLE 5—TEST DIET

Foodstuff	Quantity	Protein, Gm	Carbo- hydrate, Gm	Fat, Gm	Salt, Gm	Fluid, C c	Calories
Boiled oatmeal	100 gm	2.80	11.50	0.50			63
Sugar	10 gm		10.00				41
Milk	270 c c	9.28	13.50	11.00		270	196
Bread	60 gm	5.52	31.86	0.80			160
Butter	20 gm	0.20	16.75				158
Salt	2.3 gm				2.3		
Coffee	160 c c					160	
Water	200 c c					200	
Meat soup	180 c c					180	
Beefsteak	100 gm	27.60		7.70			185
Potato	130 gm	3.77	32.07	0.20			149
Vegetable	100 gm	0.70	9.00	1.00			21
Bread	60 gm	5.52	31.86	0.80			160
Butter	20 gm	0.20		16.75			158
Sugar	10 gm		10.00				41
Milk	20 c c	0.64	1.00	0.80			14
Pudding	100 gm	6.46	25.80	5.04			179
Water	250 c c					250	
Tea	180 c c					180	
Salt	2.3 gm				2.3		
Eggs	2 each	13.20		12.00			166
Bread	60 gm	5.52	31.86	0.80			160
Butter	20 gm	0.20		16.75			158
Tea	180 c c					180	
Sugar	10 gm		10.00				41
Milk	20 c c	0.64	1.00	0.80			14
Fruit							
Water	300 c c					300	
Salt	2.3 gm				2.3		
Total		82.2 (13 gm N)	212.5	91.7		1,720	2,064

It became early apparent, in studying small departures from the normal, that it was desirable to establish our own standards of normality under the local conditions presenting, and we, therefore, conducted observations under identical circumstances on a series of

<sup>9a</sup> Appreciation should be expressed for the skilful cooperation of Miss Martha Ziegler

<sup>10</sup> Mosenthal Arch Int Med 12:770 (Dec) 1918

nine presumably normal men mostly from the medical corps attached to the hospital. These individuals were intelligent and trained subjects accustomed to careful cooperation.

TABLE 6—MEAN WATER AND SALT EXCRETION BY PERIODS \*

Period	Water, C c		Salt, Gm	
	Normal	Arthritic	Normal	Arthritic
8-10	118	101	1 00	1 02
10-12	143	117	1 79	1 45
12- 2	161	174	1 64	1 56
2- 4	165	124	1 59	1 37
4- 6	119	111	1 41	1 20
6- 8	179	132	1 36	0 92
8-10	391	441	4 33	3 83
Total	1,279	1,201	13 12	11 36

\* The normal figures are based on the mean figures for nine cases. The arthritic figures are based on the mean figures for thirty cases.

Examination of the results of this test reveals that individual cases of arthritis occasionally show low outputs of water for the twenty-four-hour period, and sometimes retention of salt and nitrogen. The mean water output of twenty-nine arthritics shows a normal total volume of 1,200 c c, the mean salt output shows an approximately normal amount of 11 36 gm, and the mean nitrogen output shows an approximately normal amount of 11 1 gm. The rather wide range allowed to normality makes it difficult to attach importance to small departures from it. Comparison of these figures with analogous figures obtained from the normal cases studied under similar conditions, however, shows on the part of the arthritics a mean water output of about the same volume as the normals, a mean nitrogen output slightly smaller in amount, 11 1 gm, as against 12 2 gm, and a rather lower mean salt output of 11 36 gm, as against 13 12 gm for the normals. The chart represents this graphically.<sup>10</sup>

The percentage salt concentration for arthritics as compared with normals is less in four of the seven periods of the test. It is greater in two and practically the same in one. The amount by which it is less than in the normal cases is most marked in the night urine. The specific gravity is generally high. The maximum specific gravity is always above the minimum figures of from 1 018 to 1 020 accorded to normals under the conditions of the tests. The work of Mosenthal indicates that the variation in specific gravity for normals should be greater than 9 degrees. The variation of the specific gravity is less than 9 degrees in nine of the twenty-nine tests, but Mosenthal emphasizes that this is of little or no significance if the specific gravity is above 1 010, as was the case in every instance. In three of these cases the variation was more than 9 degrees when the test was repeated.

<sup>10</sup> This and the following charts were prepared by Sergt Meyer Bodansky, M C U S Army.

The variation was less than 9 degrees in Case 22, Case 53, Case 52, IV/2 (not corroborated in test of IV/3), Case 71, IV/2 (not corroborated in test of V/2), Case 57, IV/17 (not corroborated in test of IV/29), Case 48, Case 46, Case 55 and Case 62 One normal control gave a variation of less than 9 degrees, with a high specific gravity The volume of the night urine was less than 750 c c in all cases but one (Case 56), but in this instance the specific gravity and other elements were all normal Severe cases of advanced type may repeatedly

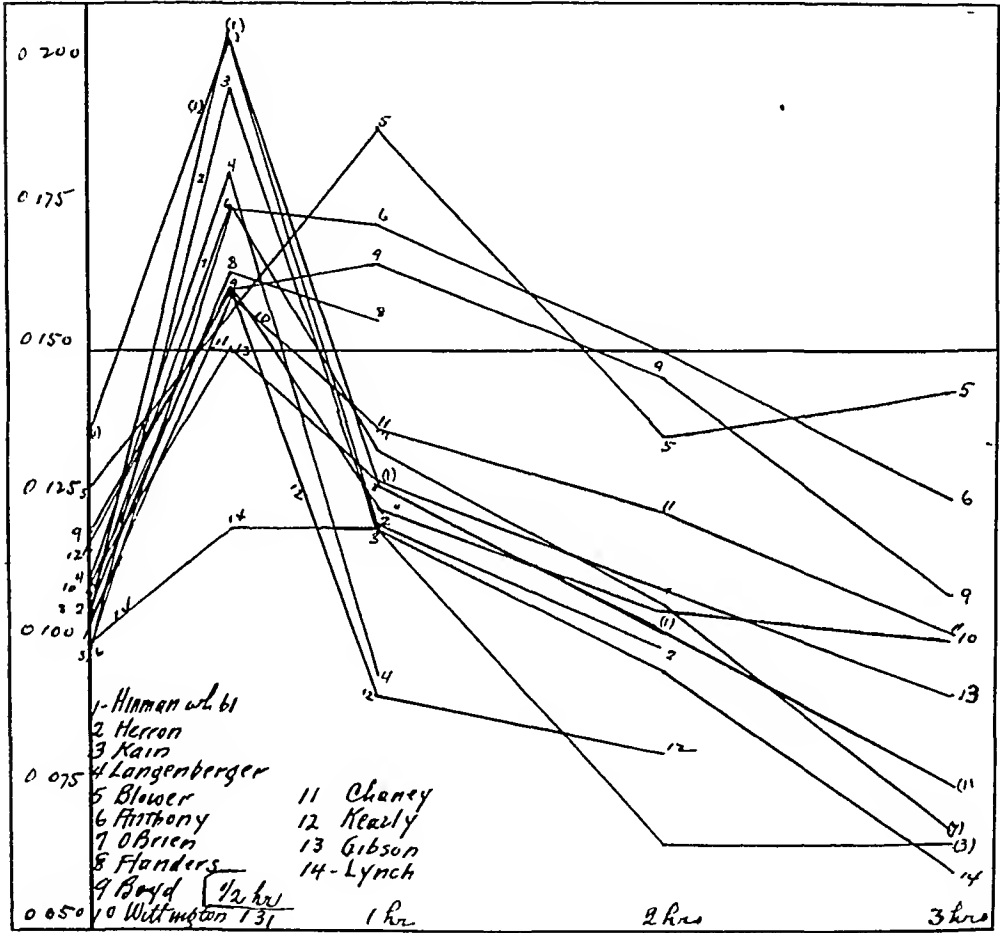


Chart 4—Lowered sugar tolerance in arthritis of moderate severity This chart and Chart 5 tend to show that the lowered sugar tolerance is somewhat proportional to the severity of the arthritis Most of the curves are importantly lower than in Chart 2

give figures by whatever standards entirely within normal limits as respects all elements of the test (Compare Case 14, March 11 and April 28, Case 7, Case 6, Case 52, Case 46 and Case 60 )

Observations were also conducted on the phenolsulphonophthalein elimination, but the results were all normal and coincided with the normal figures for this test previously recorded <sup>11</sup> Hanzlik, <sup>12</sup> in study-

11 Pemberton, R Am J M Sc 147 423 (March) 1914  
12 Hanzlik J Pharmacol & Exper Therap 9 263 (Feb) 1917

ing the salicylates, has found phenolsulphonephthalein values ranging from 55 to 75 per cent, and has concluded that renal functional efficiency is quite as good in the rheumatic as in the normal individual.

The above findings should be weighed in connection with the estimations of blood urea and noncoagulable nitrogen which were in a large series, with two exceptions, entirely within normal limits, as noted under the section dealing with this topic.

Of the more than 400 cases of arthritis studied by us in which all types and degrees were represented, only six patients had a true nephritis. The factors making for nephritis under conditions of warfare need no emphasis here, and sufficed to account for these cases.

It is to be noted, that whereas the average fasting level for blood sugar for the whole group of arthritics is slightly higher than that for normals (0.115 per cent as against 0.109 per cent or lower), the fasting level of blood urea and nitrogen for arthritics is the same as for normals. It would perhaps be of some value to conduct urea feeding tests comparable to the glucose tolerance tests with examination of the level of blood nitrogen and urea at frequent intervals after ingestion. It is to be doubted whether the disturbance which affects the utilization or removal of the glucose of the blood stream described in the next section, is confined in its influence to carbohydrate alone. There are reasons for believing it to be the expression of a widespread function in which the fats and, possibly in some degree, the nitrogenous elements may be involved.

TABLE 7—TOTAL URINARY NITROGEN

Arthritics				Normals	
Lt. Lanch	13.6	Langenberger	10.2	Pittsley	14.2
Hetherington	14.7	Tingue	10.7	Parsons	14.8
Cotter	12.4	McIntyre	10.3	Edwards	11.7
Barger	12.8	Chancy	11.9	Bollman	12.9
Langenberger	10.5	Crawford	7.1	Bodansky	11.5
Kearly	12.3	Keyes	7.2	Stricker	12.3
Hickey	9.4	Jordan	11.9	Svenarton	10.6
Jansen	11.4	Herron	12.4		
Low	14.0	McKenzie	7.9		
Mean (of 18) 11.1				Mean (of 7) 12.2	

To summarize. Charts constructed to show the response of arthritics, as compared with normals under similar conditions, to the so-called nephritis test meal indicate a very slight lag in the elimination of water, nitrogen and particularly of salt. This is hardly to be appreciated when viewed only in the light of the rather widely varying figures ascribed to normals at large. It seems fair to conclude in conjunction with the normal values found for urea and nonprotein nitrogen of the fasting blood that there is no marked dislocation of renal function in chronic arthritis, though this function may be slightly lowered in some cases.

TABLE 8—DATA AS TO VOLUME, SPECIFIC GRAVITY, SODIUM CHLORID  
AND NITROGEN IN INDIVIDUAL CASES

Name	Date	Time	Volume, Cc	Specific Gravity	NaCl per Cent	NaCl Gm	Total N, Gm
Oberg	2/26	8-10 a m	82	1 032	0 90	0 74	
		10-12 a m	140	1 033	0 89	1 24	
		12- 2 p m	56	1 035	1 06	0 59	
		2- 4 p m	118	1 034	1 20	1 42	
		4- 6 p m	157	1 028	0 86	1 34	
		6- 8 p m	55	1 039	0 98	0 54	
		Night*	354	1 033	1 06	3 75	
		Total	962			9 62	
Jaffy	3/20	8-10 a m	121	1 026	0 86	1 04	
		10-12 a m	92	1 035	1 30	1 20	
		12- 2 p m	356	1 020	0 41	1 44	
		2- 4 p m	156	1 030	0 86	1 33	
		4- 6 p m	94	1 035	0 96	0 90	
		6- 8 p m	262	1 021	0 49	1 28	
		Night	490	1 026	0 67	3 29	
		Total	1,571			10 48	
Lowe (Omitted from average)	3/5	8-10 a m	60	1 031	1 40	0 84	
		10-12 a m	92	1 035	1 71	1 57	
		12- 2 p m	63	1 042	1 47	0 93	
		2- 4 p m	108	1 036	1 23	1 23	
		4- 6 p m	89	1 038	1 20	1 08	
		6- 8 p m	51	1 037	1 16	0 59	
		Night	297	1 033	0 81	2 41	
		Total	760			8 74	
McGrann	2/5	8-10 a m	174	1 016	0 28	0 49	
		10-12 a m	180	1 019	0 52	0 94	
		12- 2 p m	300	1 019	0 57	1 71	
		2- 4 p m	142	1 030	1 06	1 51	
		4- 6 p m	144	1 030	1 05	1 51	
		6- 8 p m	163	1 021	0 42	0 69	
		Night	321	1 030	0 50	1 64	
		Total	1,431			8 49	
Hayes	2/5	8-10 a m	360	1 017	0 48	1 72	
		10-12 a m	295	1 018	0 735	2 17	
		12- 2 p m	340	1 017	0 40	1 36	
		2- 4 p m	95	1 030	0 90	0 86	
		4- 6 p m	102	1 029	0 98	1 00	
		6- 8 p m	65	1 029	1 20	0 83	
		Night	285	1 035	0 92	2 62	
		Total	1 542			10 56	
Barger	2/5	8-10 a m	73	1 027	1 07	0 78	
		10-12 a m	80	1 035	1 47	1 18	
		12- 2 p m	130	1 028	1 02	1 33	
		2- 4 p m	91	1 031	1 00	0 94	
		4- 6 p m	62	1 039	1 22	0 76	
		6- 8 p m	212	1 021	0 54	1 14	
		Night	325	1 032	1 04	3 38	
		Total	973			9 51	
Lowe	3/11	8-10 a m	102	1 028	1 38	1 36	
		10-12 a m	142	1 027	1 36	1 93	
		12- 2 p m	150	1 024	0 93	1 39	
		2- 4 p m	150	1 025	0 83	1 24	
		4- 6 p m	110	1 027	0 93	1 02	
		6- 8 p m	62	1 033	0 77	0 48	
		Night	530	1 021	0 53	2 81	
		Total	1,246			10 23	

\* From 8 p m to 8 a m

TABLE 8—DATA AS TO VOLUME, SPECIFIC GRAVITY, SODIUM CHLORIDE AND NITROGEN IN INDIVIDUAL CASES—(Continued)

Name	Date	Time	Volume, Cc	Specific Gravity	NaCl per Cent	NaCl Gm	Total N, Gm
Lau	3/25	8-10 a m	209	1 025	1 14	2 28	
		10-12 a m	112	1 030	1 50	1 68	
		12- 2 p m	116	1 030	1 27	1 47	
		2- 4 p m	158	1 031	1 20	1 86	
		4- 6 p m	60	1 025	0 72	0 43	
		6- 8 p m	112	1 030	0 93	1 04	
		Night	100	1 034	1 18	1 18	
		Total	855			9 94	
Brake	3/25	8-10 a m	150	1 035	1 69	2 54	
		10-12 a m	100	1 033	1 88	1 88	
		12- 2 p m	115	1 032	1 90	2 19	
		2- 4 p m	120	1 037	1 75	2 10	
		4- 6 p m	80	1 035	1 69	1 35	
		6- 8 p m	175	1 019	0 63	1 10	
		Night	515	1 025	0 87	4 48	
		Total	1,255			15 64	
Mrs Kain	4/1	8-10 a m	75	1 030	1 00	0 75	
		10-12 a m	75	1 035	1 48	1 11	
		12- 2 p m	100	1 033	1 34	1 34	
		2- 4 p m	100	1 033	1 24	1 24	
		4- 6 p m	48	1 029	1 22	0 59	
		6- 8 p m	113	1 032	1 28	1 45	
		Night	430	1 028	1 14	4 90	
		Total	941			11 38	
Lt Lynch	4/2	8-10 a m	54	1 029	1 14	0 62	
		10-12 a m	100	1 029	1 13	1 13	
		12- 2 p m	120	1 030	1 26	1 51	
		2- 4 p m	92	1 033	1 35	1 24	
		4- 6 p m	141	1 031	1 34	1 89	
		6- 8 p m	95	1 030	0 82	0 78	
		Night	670	1 035	0 92	6 15	
		Total	1,272			13 62	
Lt Lynch	4/3	8-10 a m	93	1 025	1 38	1 29	
		10-12 a m	135	1 026	1 50	2 02	
		12- 2 p m	130	1 027	1 40	1 82	
		2- 4 p m	110	1 030	1 42	1 84	
		4- 6 p m	135	1 028	1 18	1 59	
		6- 8 p m	235	1 020	0 54	1 27	
		Night	695	1 023	1 04	7 23	
		Total	1,533			17 06	
Crawford	4/2	8-10 a m	35	1 031	0 74	0 26	13 6
		10-12 a m	38	1 034	0 90	0 34	
		12- 2 p m	67	1 033	0 84	0 56	
		2- 4 p m	186	1 033	0 86	1 60	
		4- 6 p m	101	1 030	1 36	1 37	
		6- 8 p m	122	1 030	1 46	1 78	
		Night	545	1 030	1 64	8 95	
		Total	1 094			14 86	
Jansen	4/2	8-10 a m	50	1 035	1 34	0 67	
		10-12 a m	125	1 035	1 60	2 00	
		12- 2 p m	148	1 035	1 52	2 24	
		2- 4 p m	70	1 040	1 56	1 09	
		4- 6 p m	70	1 040	1 70	1 19	
		6- 8 p m	60	1 039	1 64	0 98	
		Night	302	1 039	1 36	4 10	
		Total	825			12 27	



TABLE 8—DATA AS TO VOLUME, SPECIFIC GRAVITY, SODIUM CHLORID AND NITROGEN IN INDIVIDUAL CASES—(Continued)

Name	Date	Time	Volume, C c	Specific Gravity	NaCl per Cent	NaCl Gm	Total N, Gm
Hetherington	4/3	8-10 a m	50	1 028	1 50	0 75	
		10-12 a m	175	1 029	1 46	2 56	
		12- 2 p m	260	1 030	1 60	3 84	
		2- 4 p m	125	1 032	1 50	1 88	
		4- 6 p m	160	1 033	1 54	2 46	
		6- 8 p m	135	1 032	1 48	2 00	
		Night	455	1 033	1 40	6 35	
Total			1,362			19 84	14 7
Cotter	4/7	8-10 a m	106	1 031	1 76	1 87	
		10-12 a m	126	1 032	1 92	2 42	
		12- 2 p m	164	1 031	1 85	3 20	
		2- 4 p m	94	1 037	1 85	1 74	
		4- 6 p m	100	1 038	1 92	1 92	
		6- 8 p m	150	1 036	1 70	2 55	
		Night	350	1 039	1 54	5 40	
Total			1 090			19 10	12 4
Barger	4/15	8-10 a m	96	1 026	1 55	1 49	
		10-12 a m	98	1 026	1 67	1 64	
		12- 2 p m	150	1 028	1 28	1 92	
		2- 4 p m	104	1 032	1 31	1 37	
		4- 6 p m	62	1 037	1 43	0 89	
		6- 8 p m	97	1 026	0 89	0 87	
		Night	315	1 030	0 94	2 96	
Total			922			11 13	12 8
Langenberger	4/17	8-10 a m	73	1 026	0 86	0 63	
		10-12 a m	75	1 027	0 90	0 68	
		12- 2 p m	116	1 026	1 12	1 30	
		2- 4 p m	200	1 025	1 08	2 16	
		4- 6 p m	155	1 024	0 86	1 33	
		6- 8 p m	242	1 019	0 44	1 07	
		Night	430	1 024	0 66	2 84	
Total			1,291			10 01	10 5
Kearly	4/19	8-10 a m	54	1 030	1 24	0 67	
		10-12 a m	98	1 029	1 40	1 37	
		12- 2 p m	242	1 019	0 56	1 36	
		2- 4 p m	208	1 024	0 82	1 71	
		4- 6 p m	106	1 029	1 05	1 12	
		6- 8 p m	180	1 012	0 12	0 22	
		Night	1,056	1 012	0 46	4 86	
Total			1,944			11 28	12 2
Miss Hickey	4/16	8-10 a m	98	1 020	1 00	0 98	
		10-12 a m	120	1 020	1 10	1 32	
		12- 2 p m	216	1 014	0 54	1 16	
		2- 4 p m	172	1 023	1 12	1 93	
		4- 6 p m	132	1 021	0 86	1 14	
		6- 8 p m	74	1 019	0 49	0 36	
		Night	490	1 023	0 64	3 14	
Total			1,300			9 93	9 4
Jansen	4/28	8-10 a m	80	1 031	1 42	1 17	
		10-12 a m	115	1 029	1 52	1 75	
		12- 2 p m	145	1 030	1 66	2 40	
		2- 4 p m	122	1 026	1 30	1 59	
		4- 6 p m	152	1 024	1 00	1 52	
		6- 8 p m	180	1 020	0 58	1 04	
		Night	265	1 032	0 80	2 12	
Total			1,059			11 59	11 4

TABLE 8—DATA AS TO VOLUME, SPECIFIC GRAVITY, SODIUM CHLORIDE AND NITROGEN IN INDIVIDUAL CASES—(Continued)

Name	Date	Time	Volume, Cc	Specific Gravity	NaCl per Cent	NaCl Gm	Total N, Gm
Lowe	4/28	8-10 a m	87	1 035	1 08	1 46	
		10-12 a m	135	1 030	1 06	2 24	
		12- 2 p m	125	1 034	1 04	2 05	
		2- 4 p m	125	1 029	1 32	1 65	
		4- 6 p m	90	1 034	1 10	0 99	
		6- 8 p m	95	1 026	0 60	0 57	
		Night	625	1 021	0 58	3 62	
		Total	1,283			12 58	14 0
Langenberger	4/29	8-10 a m	115	1 027	1 10	1 27	
		10-12 a m	115	1 020	0 90	1 04	
		12- 2 p m	180	1 018	0 80	1 44	
		2- 4 p m	185	1 014	0 40	0 74	
		4- 6 p m	175	1 016	0 66	1 15	
		6- 8 p m	180	1 020	0 88	1 58	
		Night	215	1 030	1 20	2 58	
		Total	1,165			9 80	10 2
Tingue	5/1	8-10 a m	70	1 035	1 50	1 05	
		10-12 a m	75	1 035	1 84	1 38	
		12- 2 p m	65	1 032	1 12	0 73	
		2- 4 p m	100	1 031	1 14	1 14	
		4- 6 p m	98	1 029	0 94	0 92	
		6- 8 p m	75	1 032	0 68	0 51	
		Night	550	1 021	0 70	3 85	
		Total	1 033			9 58	10 7
McIntyre	5/2	8-10 a m	85	1 038	1 62	1 38	
		10-12 a m	70	1 039	1 66	1 16	
		12- 2 p m	120	1 035	1 22	1 47	
		2- 4 p m	60	1 036	1 26	0 76	
		4- 6 p m	115	1 036	1 02	1 17	
		6- 8 p m	145	1 010	0 32	0 47	
		Night	260	1 040	0 98	2 55	
		Total	855			8 96	10 3
Chaney	5/2	8-10 a m	85	1 030	0 78	0 66	
		10-12 a m	75	1 034	1 18	0 89	
		12- 2 p m	170	1 017	0 74	1 26	
		2- 4 p m	175	1 023	0 78	1 37	
		4- 6 p m	185	1 025	1 02	1 88	
		6- 8 p m	175	1 014	0 24	0 42	
		Night	380	1 032	0 78	2 96	
		Total	1,245			9 44	11 9
Crawford	5/2	8-10 a m	175	1 014	0 26	0 46	
		10-12 a m	170	1 019	0 56	0 95	
		12- 2 p m	155	1 016	0 42	0 65	
		2- 4 p m	50	1 030	0 78	0 39	
		4- 6 p m	145	1 024	0 72	1 05	
		6- 8 p m	180	1 016	0 30	0 54	
		Night	640	1 018	0 54	3 46	
		Total	1,515			7 50	7 1
Lt Keyes	5/2	8-10 a m	45	1 030	0 80	0 36	
		10-12 a m	100	1 028	1 22	1 22	
		12- 2 p m	95	1 028	1 20	1 14	
		2- 4 p m	120	1 029	0 86	1 03	
		4- 6 p m	130	1 027	1 06	1 38	
		6- 8 p m	60	1 039	0 80	0 48	
		Night	230	1 034	1 00	2 30	
		Total	780			7 91	7 2

TABLE 8—DATA AS TO VOLUME, SPECIFIC GRAVITY, SODIUM CHLORID AND NITROGEN IN INDIVIDUAL CASES—(Continued)

Name	Date	Time	Volume, Cc	Specific Gravity	NaCl per Cent	NaCl Gm	Total N, Gm
Lt Jordan	5/2	8-10 a m	105	1 020	0 28	0 29	
		10-12 a m	135	1 025	1 02	1 38	
		12- 2 p m	480	1 013	0 28	1 34	
		2- 4 p m	115	1 030	0 98	1 13	
		4- 6 p m	100	1 032	1 06	1 06	
		6- 8 p m	135	1 021	0 48	0 65	
		Night	260	1 035	0 70	1 82	
Total			1 330			7 67	11 6
Herron	5/2	8-10 a m	95	1 033	1 56	1 48	
		10-12 a m	100	1 032	1 68	1 68	
		12- 2 p m	335	1 019	0 70	2 34	
		2- 4 p m	110	1 027	1 12	1 23	
		4- 6 p m	65	1 034	1 06	0 69	
		6- 8 p m	80	1 035	0 94	0 75	
		Night	725	1 019	0 76	5 50	
Total			1,510			13 67	12 4
McKenzie	5/4	8-10 a m	32	1 025	0 74	0 24	
		10-12 a m	120	1 026	0 92	1 10	
		12- 2 p m	65	1 026	0 52	0 34	
		2- 4 p m	115	1 030	0 94	1 08	
		4- 6 p m	60	1 030	0 64	0 39	
		6- 8 p m	58	1 030	0 46	0 27	
		Night	410	1 025	1 02	4 18	
Total			860			7 60	8 1

## NORMALS

Lynch	3/28	8-10 a m	122	1 028	1 60	1 94	
		10-12 a m	174	1 028	1 65	2 87	
		12- 2 p m	186	1 021	0 92	1 71	
		2- 4 p m	360	1 017	0 62	2 23	
		4- 6 p m	182	1 024	1 04	1 89	
		6- 8 p m	202	1 021	0 86	1 74	
		Night	315	1 031	0 76	2 85	
Total			1,601			15 23	
Jones	3/24	8-10 a m	48	1 037	1 22	0 60	
		10-12 a m	87	1 035	1 66	1 47	
		12- 2 p m	170	1 031	1 20	2 01	
		2- 4 p m	160	1 030	0 96	1 70	
		4- 6 p m	116	1 036	1 36	1 65	
		6- 8 p m	276	1 018	0 46	1 27	
		Night	440	1 032	1 20	3 19	
Total			1,317			13 14	
Bollman		8-10 a m	62	1 035	0 90	0 56	
		10-12 a m	102	1 037	1 47	1 50	
		12- 2 p m	174	1 030	1 63	2 83	
		2- 4 p m	116	1 036	1 55	1 80	
		4- 6 p m	72	1 041	1 43	1 03	
		6- 8 p m	91	1 040	1 47	1 34	
		Night	295	1 040	1 16	3 13	
Total			912			12 19	12 9

TABLE 8—DATA AS TO VOLUME, SPECIFIC GRAVITY, SODIUM CHLORID AND NITROGEN IN INDIVIDUAL CASES—(Continued)  
NORMALS—Continued

Name	Date	Time	Volume, Cc	Specific Gravity	NaCl per Cent	NaCl Gm	Total N, Gm
Bodansky		8-10 a m	105	1 031	1 76	1 87	
		10-12 a m	126	1 032	1 92	2 42	
		12- 2 p m	164	1 031	1 85	3 20	
		2- 4 p m	94	1 037	1 85	1 74	
		4- 6 p m	100	1 038	1 92	1 92	
		6- 8 p m	150	1 036	1 70	2 55	
		Night	350	1 039	1 54	5 40	
		Total	1,090			19 10	12 35
Stricker	4/16	8-10 a m	185	1 017	0 40	0 74	
		10-12 a m	225	1 021	0 62	1 40	
		12- 2 p m	330	1 015	0 28	0 92	
		2- 4 p m	275	1 020	0 70	1 93	
		4- 6 p m	165	1 024	0 94	1 55	
		6- 8 p m	310	1 017	0 40	1 24	
		Night	380	1 032	1 18	4 48	
		Total	1,870			12 26	12 4
Parsons		8-10 a m	95	1 022	0 34	0 32	
		10-12 a m	120	1 029	1 04	1 25	
		12- 2 p m	83	1 031	0 98	0 82	
		2- 4 p m	120	1 030	1 32	1 74	
		4- 6 p m	130	1 028	0 88	1 14	
		6- 8 p m	150	1 022	0 50	0 75	
		Night	325	1 032	1 12	3 64	
		Total	1,033			9 66	11 8
Pittsley		8-10 a m	290	1 020	0 62	1 80	
		10-12 a m	175	1 025	1 12	1 98	
		12- 2 p m	75	1 033	0 98	0 74	
		2- 4 p m	105	1 034	1 14	1 20	
		4- 6 p m	140	1 031	1 30	1 82	
		6- 8 p m	170	1 025	0 90	1 53	
		Night	385	1 030	0 92	3 54	
		Total	1,340			12 59	14 2
Edwards	4/18	8-10 a m	48	1 032	1 54	0 74	
		10-12 a m	108	1 033	1 70	1 84	
		12- 2 p m	168	1 031	1 60	2 72	
		2- 4 p m	104	1 032	1 42	1 48	
		4- 6 p m	92	1 040	1 56	1 44	
		6- 8 p m	128	1 036	1 37	1 75	
		Night	575	1 026	1 14	6 56	
		Total	1,230			16 47	11 7
Swenarton	5/10	8-10 a m	150	1 027	0 98	1 47	
		10-12 a m	195	1 030	1 00	1 95	
		12- 2 p m	250	1 021	0 54	1 35	
		2- 4 p m	130	1 030	0 70	0 91	
		4- 6 p m	100	1 032	1 06	1 06	
		6- 8 p m	240	1 020	0 26	0 62	
		Night	510	1 026	0 64	3 26	
		Total	1,575			10 62	13 5

TABLE 9—PERCENTAGE SALT CONCENTRATION OF ARTHRITICS AS COMPARED WITH NORMALS

Period	Normal	Arthritic
8-10 a m	0 85	1 01
10-12 a m	1 25	1 24
12- 2 p m	1 02	0 89
2- 4 p m	0 96	1 10
4- 6 p m	1 18	1 08
6- 8 p m	0 76	0 70
Night	1 11	0 87

THE BLOOD SUGAR<sup>13</sup>

It has been shown by one of us<sup>14</sup> that there is in a considerable percentage of cases of chronic arthritis a definite relation between the intake of food on the one hand, and the incidence or perpetuation of symptoms of the disease on the other. This relation is best illustrated by the fact that the institution of a reduced diet in appropriate cases may be followed by marked benefit. Of the three foodstuffs, the evi-

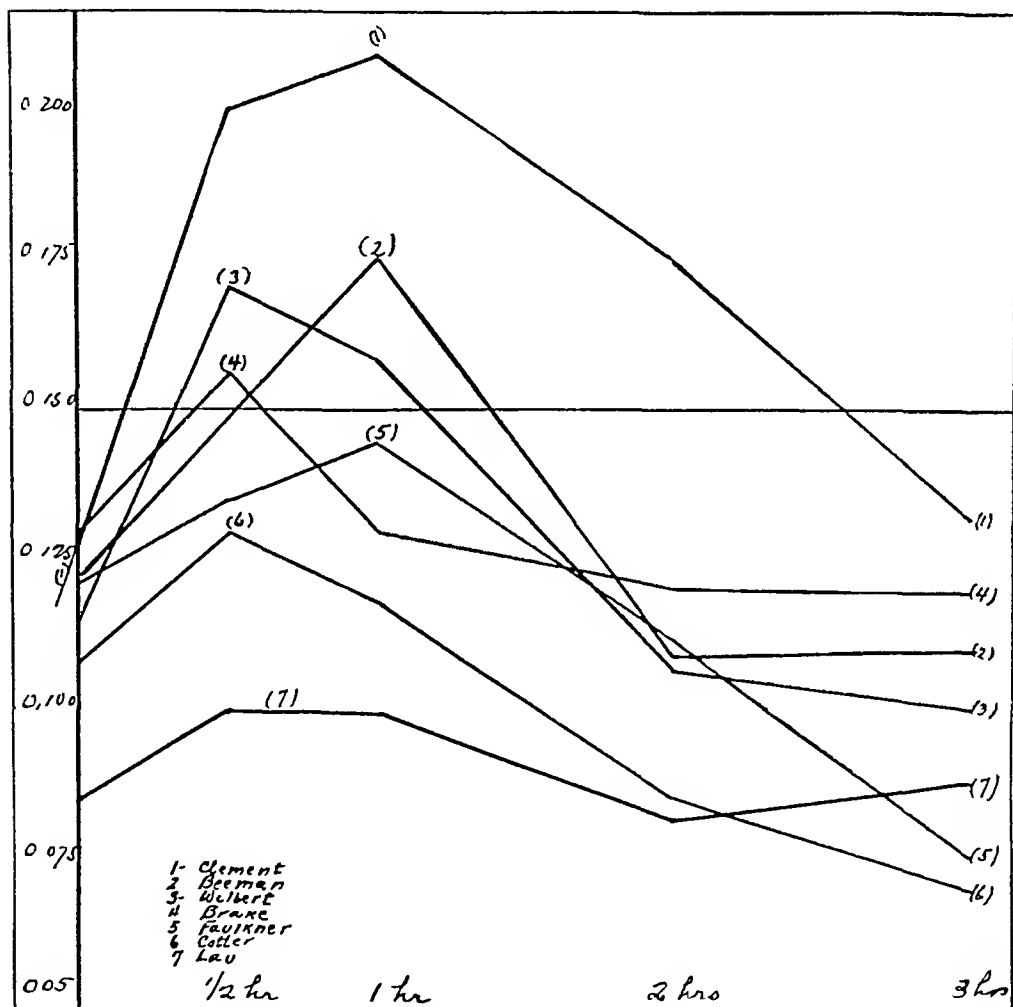


Chart 5—The sugar tolerance in mild arthritis

dence at hand, although not yet complete, has indicated that carbohydrate is most concerned in this connection. It became pertinent,

13 In addition to a report as a whole of the present studies on arthritis in the army, made before the Section on Medicine of the American Medical Association, Atlantic City, N. J., June 12, 1919, the findings regarding the blood sugar were reported in fuller detail than was possible before the American Society for Clinical Investigation, Atlantic City, N. J., June 14, 1919.

14 Pemberton, R. The Metabolism and Treatment of Rheumatoid Arthritis, *Am J M Sc* **153** 678 (May) 1917.

therefore, to determine, if possible, in the present large series whether there is a difficulty in the metabolism of carbohydrate and to this end studies were carried out in sixty cases of arthritis on the fasting level of the blood sugar and on the response of these cases to the so-called glucose tolerance test

Jacobsen<sup>15</sup> published studies on the effects of foodstuffs on the blood sugar, using the microchemical method of Bang. Adopting the principle of this method, but directing it toward the study of the carbohydrate tolerance in a variety of conditions, and using the Lewis-Benedict method for blood sugar as being better adapted to clinical use, Hamman and Hirschman<sup>16</sup> opened up an important field of investigation. Janney and Isaacson<sup>17</sup> and others have also contributed to this subject, until there has grown up a considerable and increasing literature devoted to it. The earlier method of determining sugar tolerance by estimations of the urinary sugar only has now been substituted by a combination of the two methods. One hundred and nine glucose tolerance tests were conducted by us in the present series apart from a considerable number of isolated observations on the fasting blood sugar.

#### TECHNIC

The Benedict<sup>18</sup> modification of the Lewis-Benedict<sup>19</sup> method for blood sugar was used exclusively. It has, on the whole, proved very satisfactory and well adapted to use in a long series of cases. It may be applied either to whole blood or plasma, but in the analysis of whole blood, certain precautions must be observed to insure removal of interfering substances or results will be obtained which are too high. In the picric acid-sodium picrate solution used for precipitation of the blood protein, the free picric acid alone removes the protein and other interfering substances. The amount of free picric acid is sufficient to clarify the plasma perfectly, but often it is not enough for whole blood which contains more protein. The concentration of free acid in the picric-picrate solution, therefore, must be increased in working with whole blood. This point was noted by Benedict in a recent paper<sup>20</sup>. In the present studies this trouble was encountered and remedied independently of the above publication in substantially the same way that Benedict employed, namely, by the addition of two

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15 Jacobsen *Biochem Ztschr* 56 47 1913

16 Hamman and Hirschman *Arch Int Med* 20 761 (Nov ) 1917

17 Janney and Isaacson *Arch Int Med* 20.160 (Aug ) 1918

18 Benedict, S R *J Biol Chem* 34 203, 1918

19 Lewis and Benedict *J Biol Chem* 20 61, 1915

20 Benedict *J Biol Chem* 37.503, 1919

drops of 1 2 hydrochloric acid before diluting to 25 c c with the picric-picrate solution <sup>20a</sup>

The glucose tolerance test was conducted according to the method of Hamman and Hirschman <sup>16</sup>

On the day of the test the patient eats no breakfast

At 8 30 a m samples are obtained of the blood and urine, and the patient is given 100 gm of glucose in 200 c c of water

At 9 00 a m samples are obtained of blood and urine

At 9 30 a m samples are obtained of blood and urine, and the patient is given 200 c c of water

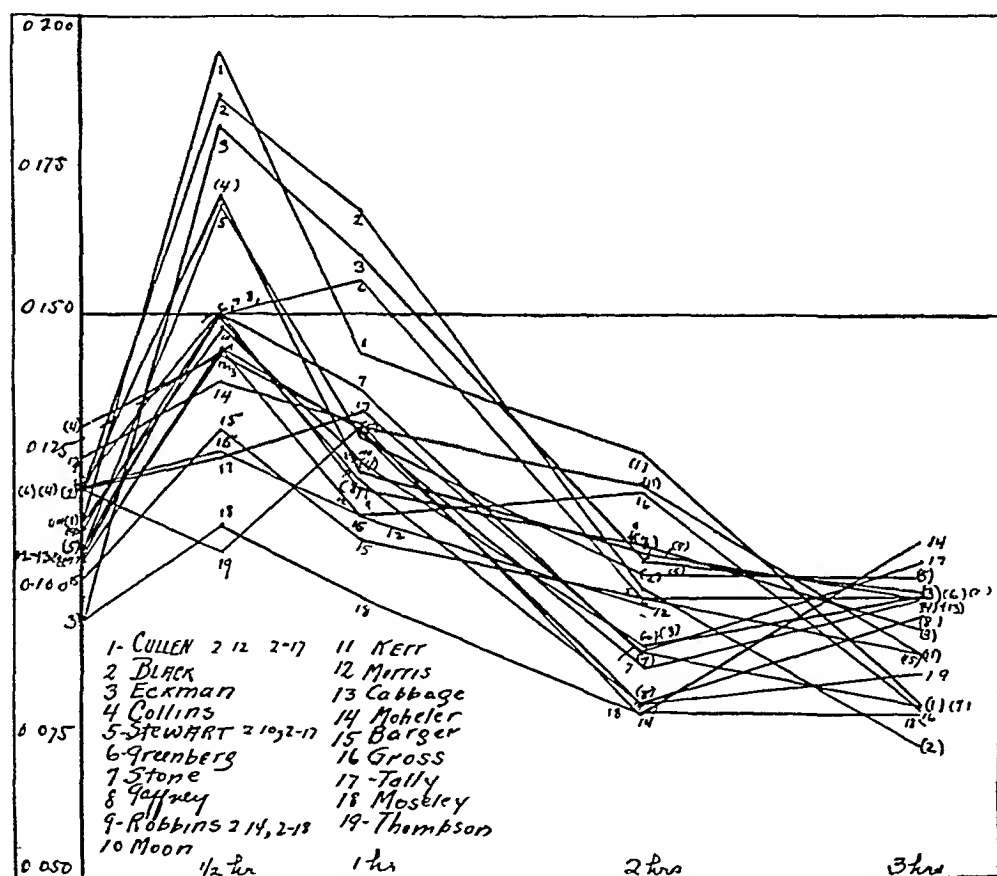


Chart 6—The sugar tolerance in convalescent arthritics In 74 per cent of these cases it was normal

At 10 30 a m samples are taken of blood and urine and the patient is given 200 c c of water

At 11 30 a m samples are taken of blood and urine

The importance of taking the blood on the half hour after the administration of glucose should be emphasized In the normal man

<sup>20a</sup> The question of the role played by creatinin in this reaction as pointed out by DeWesselow (Biochem J 13 148, 1919) and others hardly enters here as the contrasts under consideration are frequently very great, they follow immediately on ingestion of glucose and are controlled by fasting levels previously determined

this period yields the high point in the curve, the reaction is frequently complete at the end of one hour, and in many cases of slightly lowered tolerance the half hour point affords the only characteristic data. Many of the curves show a drop below the normal level at the end of the test, several cases yielding blood and plasma sugar as low as 0.065 per cent at the end of the third hour.

In the present series the renal threshold for glycosuria fell between 0.17 per cent and 0.18 per cent, which agrees with the values found by others for the normal kidney, and is something of an argument for

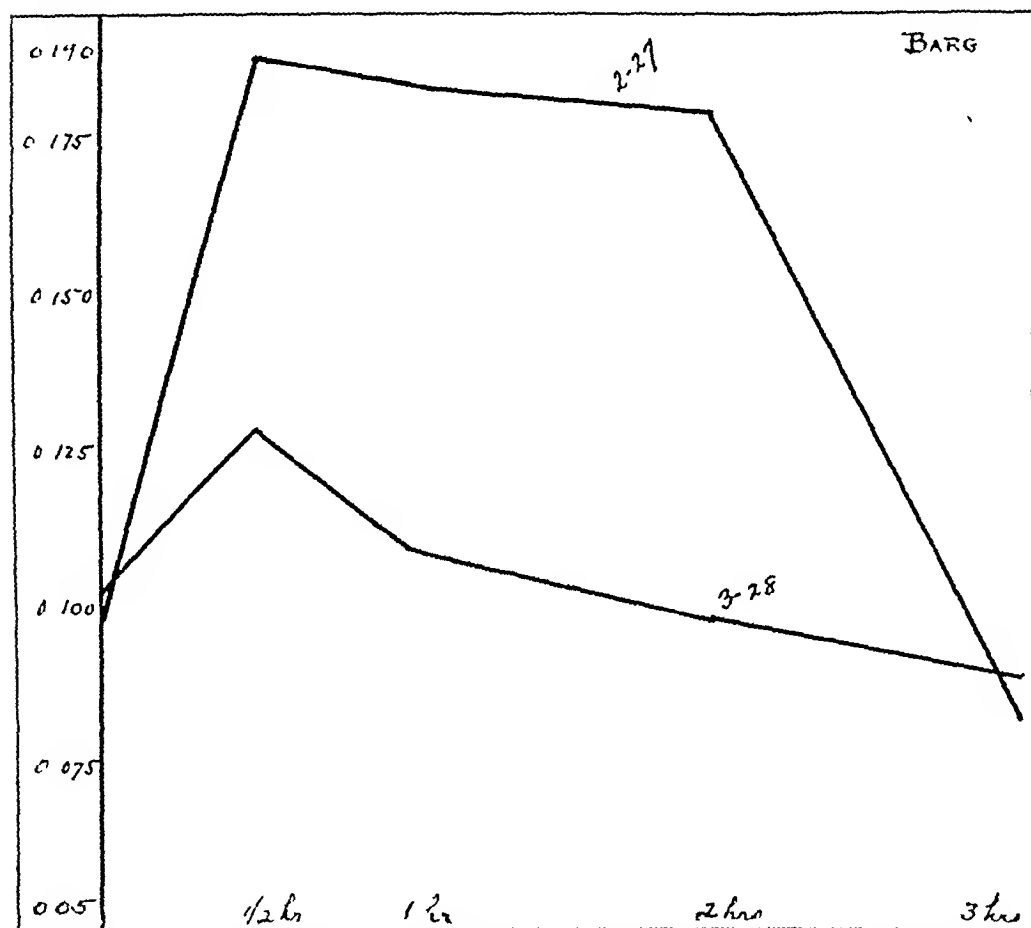


Chart 7—The striking contrast after fourteen days in the sugar tolerance of a severe arthritic who made an abrupt convalescence following tonsillectomy on March 14, 1919.

the normality of renal function in arthritis, as the threshold may be much higher in true nephritis.

On beginning our work it was soon appreciated that it was necessary to establish our own standards of fasting blood sugar and of glucose tolerance among normal individuals in view of the possibility that local conditions might influence our results, and, therefore, we conducted a series of tests on nine presumably normal persons. The results were found to fall well within the limits indicated by other workers in this field, but as our technic became perfected, we found that the average values were lower than those which we first obtained.



Chart 2 shows the curves obtained in eight normal individuals. The values range from an average fasting level for eleven normals of 0.109 per cent to an average high point for five normals of 0.140 per cent at the end of the half hour. The fasting level of sugar for the whole blood in our series falls near the upper limit of the range accorded to normality by Janney and Isaacson<sup>17</sup> (0.085 per cent to 0.11 per cent), and is slightly above the level for normals (0.10 per cent), established by Bang<sup>21</sup>.

It is pertinent to note here that single observations on the fasting level of blood sugar are open to some disturbance, possibly subjective influence, on the part of the person examined, and we were led to discard as erroneous not a few figures in cases which further study proved to be normal. By and large, the glucose tolerance test appears to give results more constantly indicative of conditions disturbing the blood sugar than do single observations. Abnormal responses occasionally follow apparently normal fasting figures and vice versa.

Glucose tolerance tests were then conducted on a series of chronic arthritics, beginning with the worst types, and at once it became apparent that there was in most of them a marked difference in their response to this test. This led us to extend our observations to a large number of cases representative of all types.

Chart 3 shows the response obtained in cases of severe arthritis, and if compared with Chart 2 the marked departure from normal is at once apparent. The values range from a fasting level of 0.113 per cent for eighteen cases to an average high point for the same number of 0.189 per cent, with many far in excess of this, three being around 0.250 per cent at the end of the half hour and hour. In the vexed field of chronic arthritis it is sometimes difficult or impossible to differentiate sharply between severe and moderate arthritis because of the fact, on the one hand, that disability may be disproportionate to the extent or severity of the disease when important joints are involved, and, on the other hand, that severe processes affecting joints less important functionally may be tolerated easily for long periods. Furthermore, accurate classification of the types of arthritis is sometimes impossible or can be made after the lapse of time only. Thus the lowest curve on Chart 3, is probably improperly placed there and is that of a case of apparently noninflammatory bone atrophy with edema of the soft tissues. This apparent exception was maintained in repeated tests, and was reconciled with difficulty until the clinical diagnosis became apparent at a late date.

An attempt was also made to segregate arthritics into groups of severe and moderate, but for the reasons just indicated this classifica-

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21 Bang. *Der Blutzucker*, Wiesbaden, 1913.

tion can be only approximate. Charts 4 and 5 illustrate this attempt and show marked departures from normal in most instances. In general, it can be said that the height of the sugar curve, that is to say, the degree to which the sugar tolerance is lowered, is largely proportional to the severity of the active process per se. Severity of the process apparently plays as big a rôle as does the extent of the process in affecting the tolerance. Some of the curves on Charts 4 and 5 fall within or only slightly above normal values. In general, these excep-

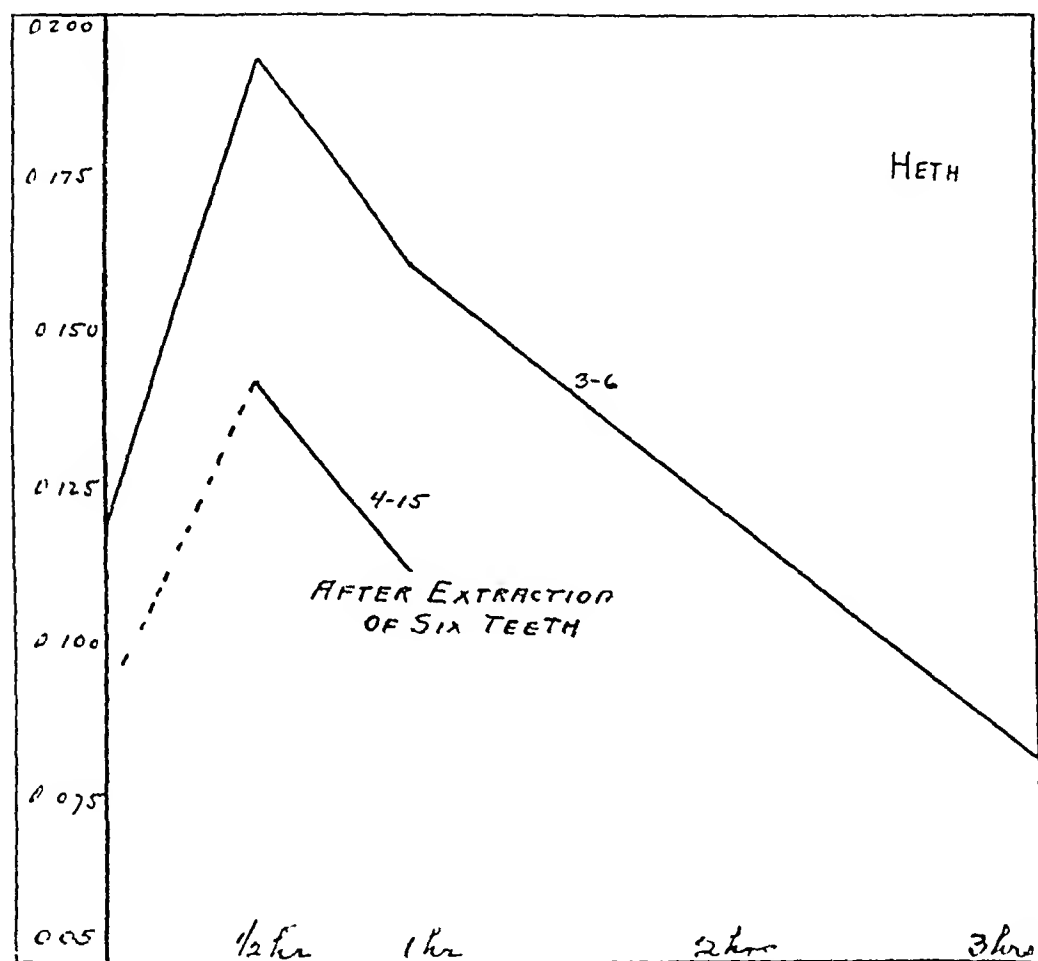


Chart 8 — The contrast in sugar tolerance of a spondylitis patient who recovered after the extraction of six teeth

tions occur in patients who have passed the zenith of their trouble and who show a tendency to convalesce, or they occur in cases in which the distribution and severity are limited. No fixed rule exists, however, and the parallelism is not exact, although it is surprisingly close. In some apparently severe cases there is a normal or only slightly disturbed sugar tolerance. It should be borne in mind that the glucose tolerance test is merely a gross way of ascertaining deviation of a function which is probably complex and dependent on factors

not understood, and that it is not necessarily adjusted to reflect a lowered tolerance in all cases. Furthermore, as just noted, there is no absolute standard of severity of the arthritic process.

A group of twenty convalescent arthritics was then studied. These patients were representative of a severe and generally long continued arthritis, and at the time were free from symptoms. It was found that this group gave curves the average of which was importantly lower than the severe or moderate cases, falling with some exceptions (five out of nineteen cases) pretty well within long limits. That is, 74 per cent of the group of convalescents gave a normal tolerance. It is clear, therefore, that the average curves for the moderate and mild cases can be made to vary somewhat according as the cases are classified, but by any standards the sugar tolerance tends to return to normal as convalescence proceeds. The details of certain cases in these several series will be considered later, after discussion of the field as a whole. In general, our high curves were marked more by the height to which they rose and the abruptness of the rise than by their duration at a high level, although there were some noteworthy exceptions. By and large, the higher the curve, the slower the return to normal, but it is obvious that by increasing the abscissae the curves could be made to appear flatter and indicative of a more delayed return.

On attempting to relate this disturbance to some of the other factors known to influence chronic arthritis, we conducted a series of determinations on the tolerance during the ill health and convalescence of the same individual following various procedures. It was found that there was an abrupt change in the sugar tolerance in cases which improved after removal of apparently causative foci of infection. Thus Chart 7 illustrates in a striking manner the contrast after twenty-nine days in the sugar tolerance of a soldier (Case 45) the subject of an intense arthritis of long standing in the left hip and foot, who made an abrupt and marked convalescence following tonsillectomy. The curve showing a normal tolerance was obtained fourteen days after the tonsillectomy.

Chart 8 illustrates the same thing in a man (Case 46) 40 years of age, with arthritis and tenderness of the entire spine and changes shown by the roentgen ray, who underwent marked clinical improvement after the removal of six abscessed teeth. The higher curve was obtained March 6, and the lower curve April 15.

Chart 9 shows curves representing the averages, respectively, of two tests taken during ill health, and of two during distinct convalescence in a line officer (Case 1), the subject of a widespread myositis and arthritis which had entirely incapacitated him. He had had a possible focus in a tooth removed about two months before the first curve

was obtained, and was in a stationary condition. Clinically he made a full recovery on dietary lines alone, as described under the section dealing with dietetic measures. The two averaged curves represent an interval between them of approximately two months.

In the group of convalescents illustrated in Chart 6, it is to be noted that these soldiers convalesced in large part in the presence of demonstrable surgical foci of infection, which suggests, in the light of the proportion of cases of arthritis at large which show lowered sugar tolerance, that the disturbed tolerance may return to normal as the patient improves, even without the removal of the focal infection. At least five persons giving normal tolerance curves were the subjects of demonstrable surgical foci. As noted above, about 26 per cent of convalescent arthritics (five in number) still gave a lowered sugar tolerance. Three of these five still had demonstrable surgical foci.

Chart 10 (Case 50) illustrates a case of chronic but mild arthritis of one knee, in an officer with a slightly lowered tolerance, who made a slow but definite improvement following repeated injections of non-specific protein. He was apparently free from focal infection. This chart suggests, but lacking further evidences does not prove, that the lowered tolerance was restored to normal by these measures. The curves are a month apart.

Chart 11 (Case 61) represents the curves obtained during an acute febrile attack of arthritis in several joints. The highest curve was taken before treatment was instituted. The lower was obtained after the relief of symptoms by full dosage of acetylsalicylic acid. The second curve is lower than the first, but it is probable that the difference between them represents nothing more than the limitations of the method. It is clear that no important correction of the disturbed tolerance took place, though such change as did occur, was in keeping with other evidences of the tendency toward the return to normal with improvement of the arthritis. Further observations are desirable on this point. The lowest curve shows the tolerance at nearly a normal level a week after tonsillectomy, when the patient had made a complete recovery from the arthritis. The dates of the curves from above downward are respectively, April 21 and 24, and May 13.

Another experiment was conducted on the effect of acetylsalicylic acid on blood sugar, supplementing the observation made in Case 61 recorded on Chart 11. Two subjects of advanced arthritis, one improving and one stationary, were given 15 grains of acetylsalicylic acid under fasting conditions, after which the blood sugar was determined at frequent intervals, but as indicated in Table 10 there was no change in the sugar level. This is in essential agreement with the other experiment just quoted.

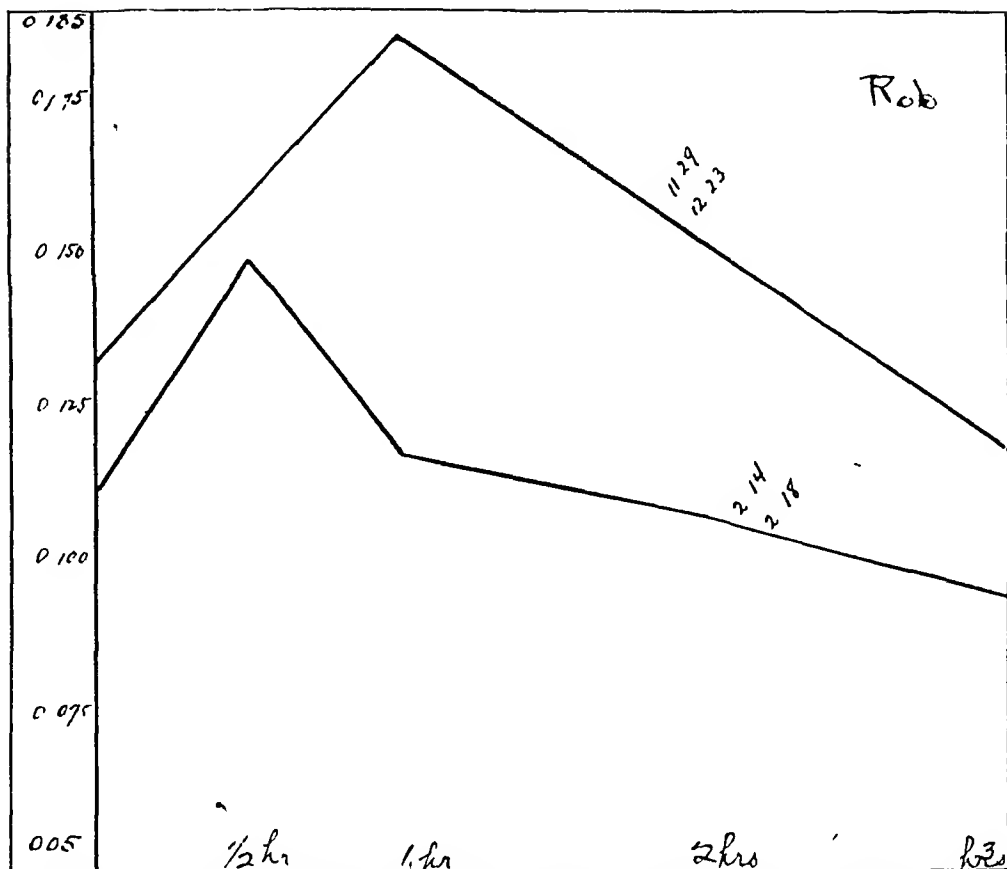


Chart 9—The contrast in sugar tolerance before and after convalescence on a restricted diet

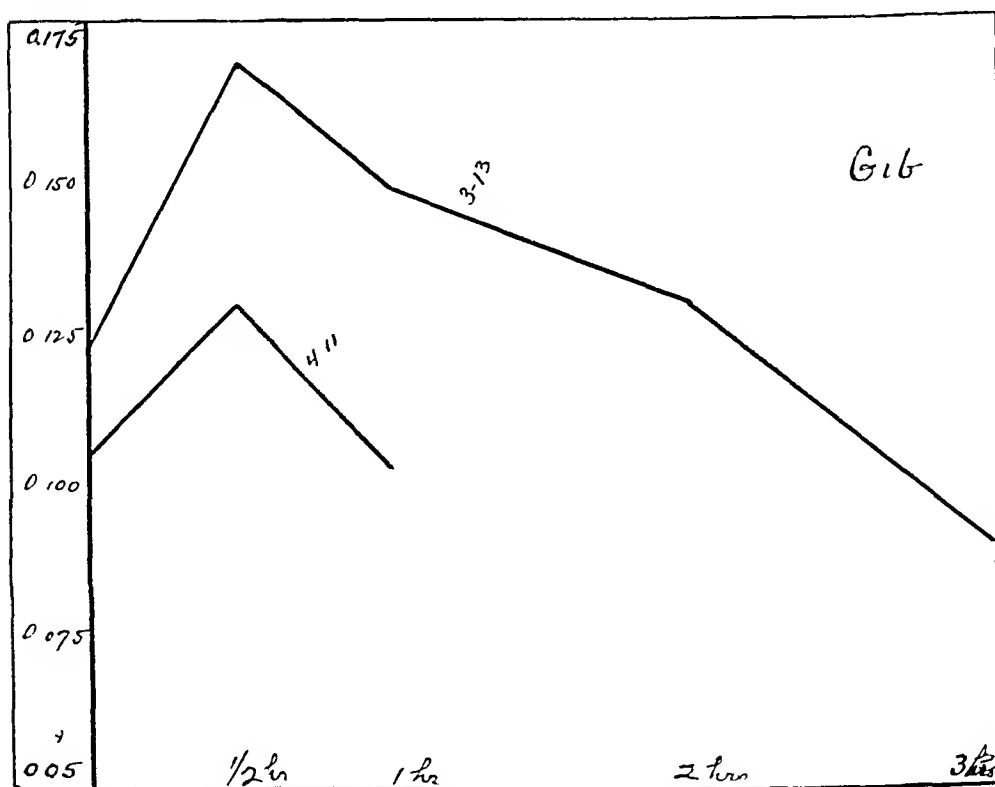


Chart 10—the contrast before and after treatment by nonspecific protein injections

TABLE 10—EFFECT OF ACETYSALICYLIC ACID ON BLOOD SUGAR (FEB 22 1919)

	Invy Case 7		Low Case 14	
	Blood per Cent	Plasma per Cent	Blood per Cent	Plasma per Cent
8 G	0.101	0.097	0.115	0.115
9 G	0.104	0.105	0.110	0.115
9 G (15 grains of acetylsalicylic acid to each)	0.108	0.110	0.110	0.110
10 G	0.105	0.110	0.108	0.112
10 G	0.109		0.105	0.112
12 G	0.107	0.109	0.110	0.113

Chart 12 (Case 22) illustrates a distinctly lowered sugar tolerance in a case which made striking improvement because of a sharp dietary, in the presence of a surgical focus. This case also will be described in detail under the section on diet. The curve next to the highest is

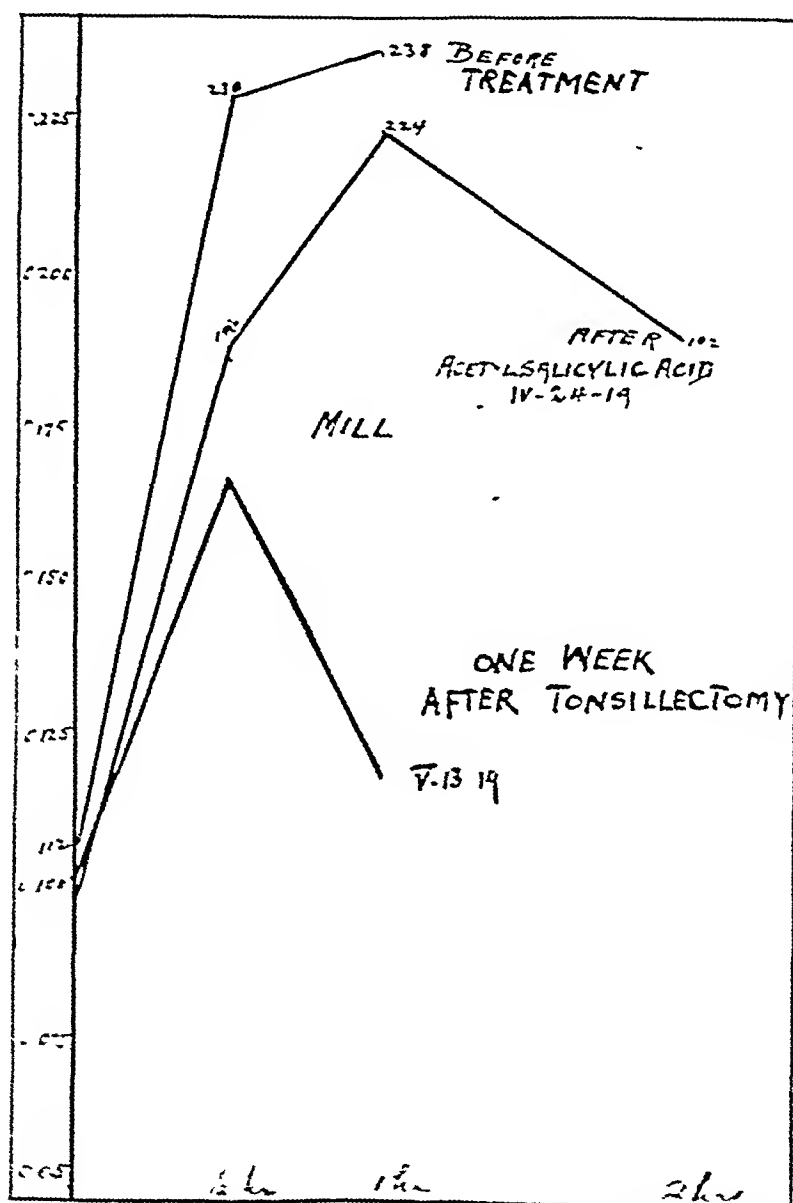


Chart 11—The slight effect of acetylsalicylic acid and the marked effect of tonsillectomy in a severe case which recovered

that obtained when this soldier was at the height of his trouble, which consisted in almost complete ankylosis of both hips, knees and spine, together with great limitation of function in the left shoulder The roentgen-ray evidence was widespread and great The third and fourth highest curves were obtained when the soldier had made an emphatic

TABLE 11 — ARTHRITICS CLASSIFIED FOR PURPOSE OF CHARTING AS FOLLOWS

Severe	Moderate	Mild
Case 6—Hayes 4—McGrann 45—Barger 46—Hetherington 48—Jansen 13—Lummis 15—Studebaker 16—Bryce 10—Massood 8—Martin 2—Haberle 1—Robbins (1 and 2) 20—Wasson 14—Lowe 7—Jaffy 61—Miller 62—McKenzie 22—Oberg	Case 11—Hinman 50—Gibson 3—Blower 12—Boyd 23—O'Brien 21—Whittington 52—Lt. Lynch 53—Mrs. Kain 54—Miss Anthony 56—Kearly 57—Langenberger 59—Flanders 47—Chaney 60—Herron	Case 17—Faulkner 43—Wilbert 44—Brake 9—Beeman 51—Lau 55—Cotter 79—Cox 36—Clement (1)

TABLE 12—MEAN FASTING LEVELS FOR THE SEVERAL GROUPS

Group	No of Cases	Blood	No of Cases	Plasma
Normals	11	109	1	097
Convalescent arthritides	16	115	21	114
Severe arthritides	15	116	13	115
Moderate arthritides	13	112	11	110
Mild arthritides	6	115	8	121
Other pathologic types			3	118

TABLE 13—SUGAR TOLERANCE FOR NORMALS

Name	Date	Fasting		Half Hour		One Hour		Two Hour		Three Hour	
		Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Plasma	Blood
Bodansky	12/27	108				122		092		101	
Foster	12/27	110				115		124		097	
Edwards	12/27	104		138		109		107		099	
Jones	1/ 3	101		147		147		115		098	
Smith	1/ 3	111		158		104		094		083	
Hudson	3/14	103									
Edder	3/14	100									
Meador	12/28	112				127		115		115	
Carter	1/29	128		138	136	114	109	095	088	098	088
Outshall	12/28	122				125		114		083	
Monahan		097	097	120	122	094	088				
Mean of 9		109		140		117		107		097	

\* In order to save space, the tables showing the presence or absence of glycosuria for each of the periods in the following tests are omitted The threshold value fell between 0.170 and 0.180

TABLE 12.—SUGAR TOLERANCE FOR ANTHROPIES

Name	Date	Fast		Half Hour		One Hour		Two Hours		Three Hours	
		Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma
Blover	12/10		127			182		187		147	
Beeman	12/15	123				175		174		116	
Boyd	1/9	119		160		165		146		173	
Iumme	1/9	107		170		122		167		151	
Strickland	1/16	144		221		192		161		132	
Baker	1/16	170		212		225		200			
Mascoe	12/21	206				212		212		167	
	1/2	124									
	1/6	144		168		220		188		117	
Mason	12/22		161			16		17		147	
	12/27	130		175		127		125			
	3/5	165	160	168	208	180	204	185	180	180	187
Haberman	12/10		150			170		170		170	
	1/17		160		120		120		120		161
	2/7	162									
O'Brien	2/4	120		175	175	147	173	114	107	157	167
Robbins	11/29		125				188		167		167
	12/29		142				185		140		154
	12/30	160									
	2/14	107	110	120	122	117	120	107	104	103	108
	2/18	115	115	160	167	120	115	118	111	110	103
	4/11	166	166	124	125	164	171				
Wittington	1/21	110				161		123		160	
	2/4	123	123	178	190	171	120	115	108	101	100
Watson	1/29	117	115	181	181	100	136		126		
	2/8	164	160	170	182	144	144	160	160	115	115
Lowe	1/12	146		250		177		120		174	
	2/22	113	118								
	5/11	168		200	214	167	163				
Jaffy	12/11		107			246			181		133
	2/22	161	107								
	3/7	100									
Faulkner	1/22	128	122	120	155	140	144		112	100	105
Haves	12/11	136					178		121		109
	12/20	128									
	2/6		135								
	2/17	133	132	165	231	250	250	175	173	101	135
	5/9	160		170	182	185	192				
McGowan	12/10		107				221		172		167
	2/7	162									
Oberg	1/31		107		183		160		161		160
	2/4	114	107	228	246	214	220	206	200	107	164
	3/2	160	164	214	228	278	294	312	325	250	278
	5/14	162	160	160	160	187	190	200	197	171	173
	4/25	112	108	181	185	200	208	186	140		
	5/8	115	112	160	183	100	105				
Hamman	12/2	135									
	1/6	123		203		125		102		105	
Wilbert	2/21	120	115	162	170	158	158	107	107	161	160
Brake	2/21	125	120	152	156	181	123	125	121	120	
Birger	2/27	164	160	170	190	182	186	177	181	164	
	3/28	163	160	128	120	110	111	101	100	101	
Hetherington	3/5	122	124								
	3/6	115	120	188	195	170	167			151	160
	4/15			141	143	114	113				
Jensen	3/6	115	117	177	181	158	174	105	105		
Gibson	3/13	125	125	173	171	155	170	144	131	104	101
	4/11	165	167	127	131	167	164				
Lat	3/22	165	163	168	160	166	160	161	162	167	168
Lt Lynch	3/22	160	160	118	120	120	120	167	165	165	160
Mrs. Kahan	3/22	162	168	188	190	116	120	162	160	165	165
Miss Anthony	3/26	160		174		172		170		123	
Cotter	4/2	110	108	128	120	117	118	108	106	105	100
Kearse	4/6	115	117	153	161	160	161	160	161		
Langenberger	4/15	111	111	172	180	160	164				
Brano	4/15	121	123	160	171	156	170				
(after exercise)	4/19	112	111	178	180	111	111	105			
Flanders	4/19	168	167	184	193	153	170				
Cox	4/19	128									
Chambers	4/20	168	168	135	141	160	165	175	170		
	5/6	162	163	138	160	137	137	114	123	160	161
Heron	4/20	160	165	188	185	151	121	170	168		
ML	4/21	167	112	224	220	228	228				
	4/24	167	160	188	190	214	214	177	170		
	5/13	174	163	165	120	140					
	4/28	115	115								
Lord	5/11	176	167	188	184	163	163				
Folger	5/18	110	110	210	218						
McKenzie	4/29		122		215		188				

\* The analyses in the cases marked with an asterisk were made under the direction of Mrs. M. B. Washburn who was associated with Capt. F. M. Allen on the date of the analysis. The writers desire to express their obligation for this and other courtesies.



that obtained when this soldier was at the height of his trouble, which consisted in almost complete ankylosis of both hips, knees and spine, together with great limitation of function in the left shoulder. The roentgen-ray evidence was widespread and great. The third and fourth highest curves were obtained when the soldier had made an emphatic

TABLE 11 — ARTHRITICS CLASSIFIED FOR PURPOSE OF CHARTING AS FOLLOWS

Severe	Moderate	Mild
Case 6—Hayes 4—McGrann 45—Barger 46—Hetherington 48—Jansen 13—Lummis 15—Studebaker 16—Bryce 10—Massood 8—Martin 2—Haberle 1—Robbins (1 and 2) 20—Wasson 14—Lowe 7—Jaffy 61—Miller 62—McKenzie 22—Oberg	Case 11—Himm in 50—Gibson 3—Blower 12—Boyd 23—O'Brien 21—Whittington 52—Lt. Lynch 53—Mrs. Kain 54—Miss Anthony 56—Kearly 57—Langenberger 59—Flanders 47—Chaney 60—Herron	Case 17—Faulkner 43—Wilbert 44—Brake 9—Beeman 51—Lau 55—Cotter 79—Cox 36—Clement (1)

TABLE 12—MEAN FASTING LEVELS FOR THE SEVERAL GROUPS

Group	No of Cases	Blood	No of Cases	Plasma
Normals	11	109	1	097
Convalescent arthritics	16	115	21	114
Severe arthritics	15	116	13	115
Moderate arthritics	13	112	11	110
Mild arthritics	6	115	8	121
Other pathologic types			3	118

TABLE 13—SUGAR TOLERANCE FOR NORMALS

Name	Date	Fasting		Half Hour		One Hour		Two Hour		Three Hour	
		Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Plasma	Blood
Bodansky	12/27	108				122		092		101	
Foster	12/27	110				115		124		097	
Edwards	12/27	104		138		109		107		099	
Jones	1/ 3	101		147		147		115		098	
Smith	1/ 3	111		158		104		094		083	
Hudson	3/14	103									
Edder	3/14	100									
Meador	12/28	112				127		115		115	
Carter	1/29	128		138	136	114	109	095	098	098	088
Cutshall	12/28	122				125		114		083	
Monahan		097	097	120	122	094	088				
Mean of 9		109		140		117		107		097	

\* In order to save space, the tables showing the presence or absence of glycosuria for each of the periods in the following tests are omitted. The threshold value fell between 0.170 and 0.180.

TABLE 14—SUGAR TOLERANCE FOR ARTHRITIS

Name	Date	Fast-ing		Half Hour		One Hour		Two Hour		Three Hour		
		Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	
Blower	12/10*		127			175	188	135		110	143	Omitted from aver
Beeman	12/26	123		160		165		109		108		
Boyd	1/ 9	119		179		123		146		081		
Lummis	1/ 9	107		221		192		100		132		
Studebaker	1/16	144		212		250		161		167		
Bryce	1/16	150				262		200				
Massood	12/31	203						212				
	1/ 2	124		168		220		188		113		
	1/ 6	144								147		
Martin	12/22*		161	175		125	166	125	156	188	185	
	12/26	120		198		186		185		150	150	Entered on "convalescent" also After exercise
	3/ 5	106		109		120		120		120	080	
Haberle	12/10*		102	175		147		114		107	068	
	1/17		120			188		140		167	107	
	3/ 7					185					134	
	2/ 4			125								
O'Brien	11/29*		142								088	
Robbins	12/23*										103	
	12/30	109		110	130	117	120	107	104	093		
	2/14	107		115	169	120	115	118	111	110		
	2/18	118		106	134	136	094					After fasting Just before tonsillectomy A week after tonsillectomy
	4/11	106		110		161						
Wittington	1/31	123		123	178	190	131	126	115	106	100	
	2/ 4	117		115	181	181	139	136		108	091	
Wasson	1/29	094		100	150	153	144	144		136	086	
	3/ 8	146		118	250					115	115	
Lowc	1/13	113		108	200	214	167	163		100		
	2/22	108		107				246		181		
	5/11	108		097								
Jaffy	12/11*	101		122	130	135	140	144		112	099	Before tonsillectomy After tonsillectomy
	2/22	109						178		121	075	
	3/ 7	128									079	
	1/22	136										
Faulkner	12/11*	123		135		195	201	250	175	173	101	
Hayes	12/26	133		108	179	182	185	192		172	107	
	2/ 6	109		097				231				
	2/17	109										
	5/ 9	102		097		183		160		101	089	
McGrann	12/10*					246	214	239	206	203	067	
	2/ 7	106		097	238	238	278	291	312	326	259	Six teeth out about 4 weeks ago Protein injection 5 days ago, feels better now
	1/31	114		094	169	169	187	190	200	197	071	
Oberg	2/ 4	093		103	181	185	200	208	156	140		
	3/ 2	102		108								
	3/14	112										
	4/25											
	5/ 8	115		112	150	153	100	096				
	12/ 2	135										
Hinman	1/ 6	123		103	162	170	125	158	102	107	075	
	2/21	129		115	152	156	131	129	107	121	101	Also on convalescent sheet
Wilbert	2/21	104		100	179	190	182	186	107	125	120	
Brake	2/27	103		103	128	130	110	111	101	101	084	
Barger	3/28	122		124								
	3/ 5	115		120	188	195	169	167				
	3/ 6	115			141	143	114	113				
Hetherington	4/15	117			177	181	158	174	095	095	091	
	3/ 6	115			173	171	155	150	144	131	094	
	4/15	125			127	131	107	104				
Jansen	3/13	105										
Gibson	4/11											Before aspirin Symptoms relieved by aspirin A week after tonsillectomy Arthritis, empyema, febrile (101 F) Febrile, 100/2, no aspirin
	3/22	085		086	098	098	100	096	099	081	082	
	3/22	100		100	118	120	120	120		096	097	
Lau	3/26	099		098	174	172	116	118	088	086	060	
Lt Lynch	4/ 2	110		108	128	129	109	091	086	081	065	
Mrs Kain	4/ 6	115		117	153	161	100	094			125	
Miss Anthony	4/15	111		111	172	180	156	150			075	
Cotter	4/15	121		123	169	171	111	111				
Kearly	4/16	112		111	138	140	155	155				
Langenberger	4/19	108		107	154	163						
Bruno	4/19	128										Also on convalescent sheet
(after exercise)	4/19	108										
Flanders	4/20	108		108	135	141	160	137	135	130	100	
Cox	4/20	102		103	158	160	137	121	114	123	098	
Chaney	3/ 6	104		105	188	205	131	238	197	192		
	4/20	104		112	224	230	238	224				
	4/21	107		100	188	190						
Herron	4/24	097										
Miller												
	5/13	104		103	165	123	119					
	4/28	115		115								The analyses in the cases marked with an asterisk were made under the direction of Miss M B Wishart, who was associated with Capt F M Allen on the diabetic service of the hospital. The writers desire to express their obligation for this and other courtesies
	5/11	108		107								
	5/18	110		110								
Lord	4/29											
Folden												
McKenzie												

\* The analyses in the cases marked with an asterisk were made under the direction of Miss M B Wishart, who was associated with Capt F M Allen on the diabetic service of the hospital. The writers desire to express their obligation for this and other courtesies

therapeutic advance following diet. The lowest curve represents the return of the sugar tolerance to practically normal limits, following the removal of a necrotic pair of tonsils, after he was well on in convalescence and able to walk with crutches.

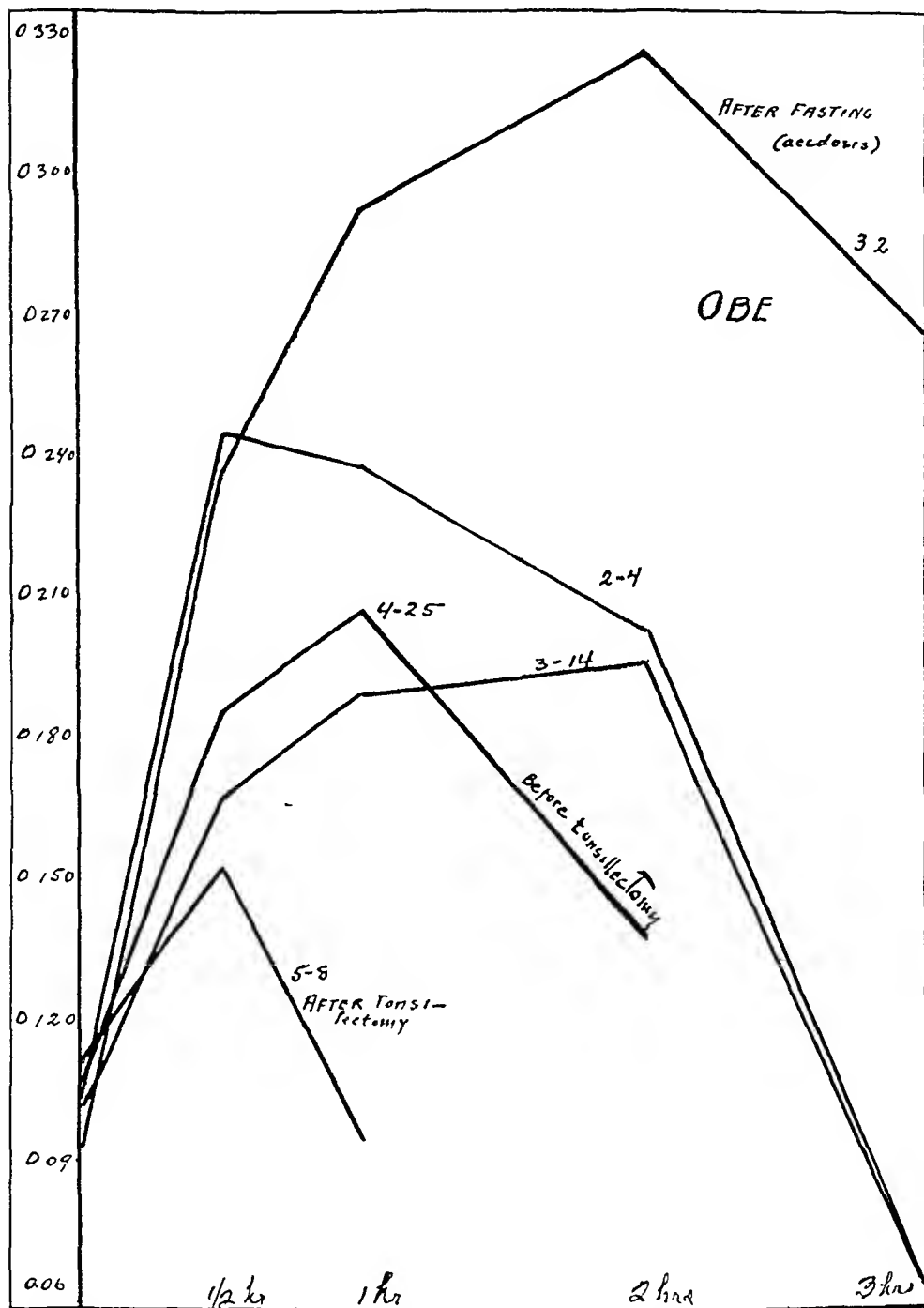


Chart 12—The lower four curves show the tendency of a lowered tolerance to return to normal following improvement under diet and, later, tonsillectomy (see text for details)

Therefore it seems clear that as cases of arthritis improve, irrespective of the therapeutic measure to which this is due, the lowered sugar tolerance tends strongly to a return to normal. It seems to do so most rapidly, however, after surgical removal of the causative infection.

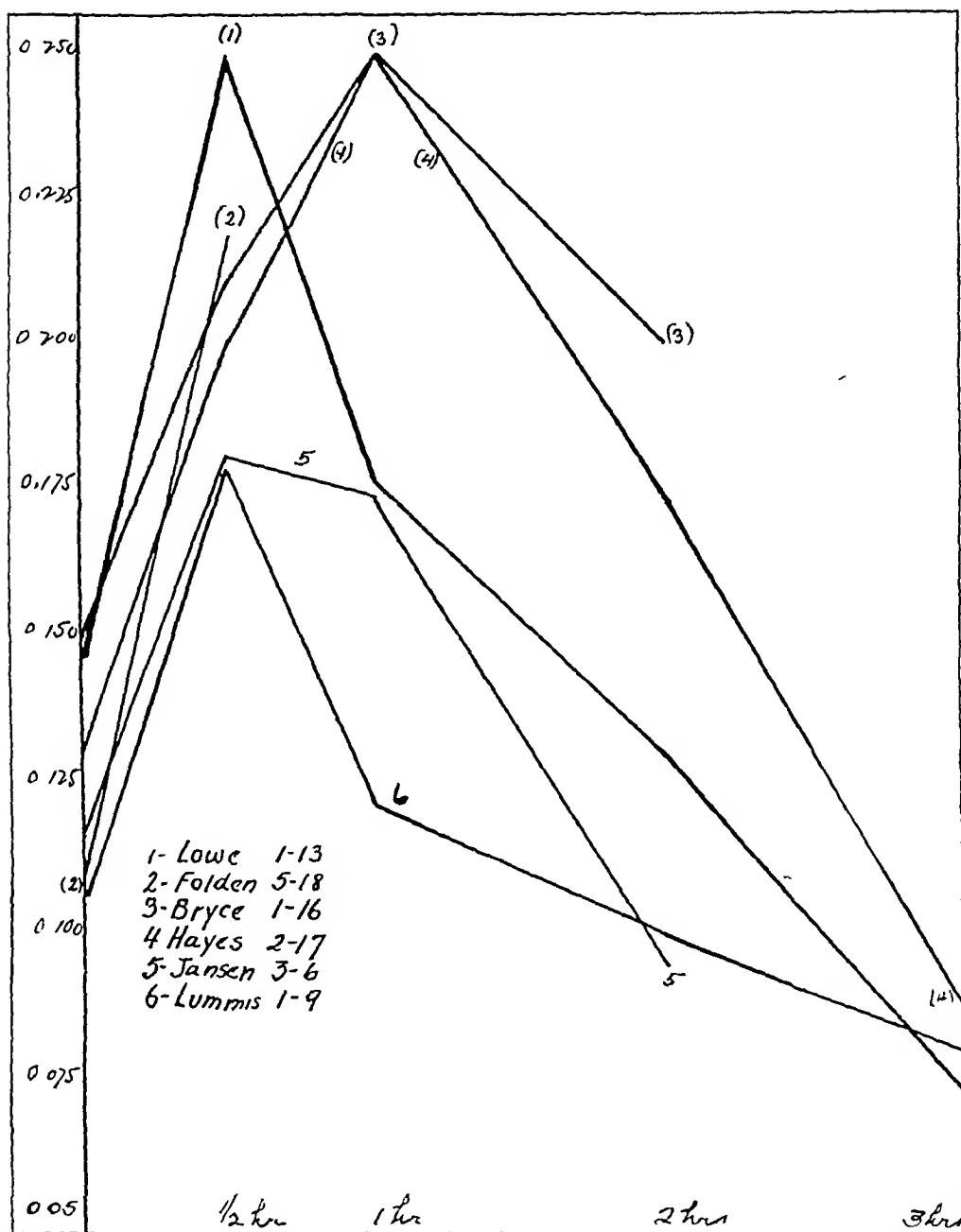


Chart 13—The persistence of lowered sugar tolerance in chronic cases from which all demonstrable foci of infection had been removed

Our experience suggests that the sugar tolerance test may sometimes be helpful to indicate whether all foci have been removed. For example, a case of active arthritis of moderate chronicity may fail to

improve after the removal of dental foci. If the tonsils in such a case are apparently normal, as often happens, the maintenance of a definitely lowered sugar tolerance would suggest that foci are still operative and presumably in these tissues. Other applications are obvious and may later be justifiable, but at present there are too many variables to warrant much emphasis, except within narrow limits. It must be borne in mind that long standing cases from which all demonstrable foci have been removed may retain their lowered tolerance.

Chart 13 represents high curves obtained in a series of cases from which all demonstrable surgical foci had been removed. It is, of course, impossible to say that any person is free from a focus of infection, and it may be that the high curves of this chart indicate greatly lowered sugar tolerance referable to hidden foci. The presumptive evidence, however, is to the opposite effect, especially as it is well recognized that in long standing cases the removal of foci may be followed by less gratifying results, or failure, and it is, perhaps, easier to believe that the persons in question have suffered a dislocation of physiologic function which persists after the removal, or is independent, of focal infection. Thus the high single peak occurred in a soldier (Lowe, Case 14) who had been ill more than two years, who had had his tonsils removed months before, who had no pathology in his mouth or genito-urinary tract, and who had had attention to his sinuses as well. This case was very refractory to all kinds of treatment, of which he had had thirteen different varieties, including nonspecific protein injection, a brief period of diets and hydrotherapy.

Curve 3 (Br, Case 16) is that of a civilian, 45 years of age, studied by permission of the commanding officer. He had been under observation for about four years, for the first year or two of which he had been examined and treated from every angle for the removal of focal infections. Failing relief by all these methods, he made a gratifying improvement, which amounted to recovery, along dietary lines. Curve 4 (Hayes, Case 6) is that of another regular army man who had been ill about two years. He had been treated at Hot Springs and had had his tonsils removed four or five months previous to this observation, having at the time no other detectable surgical infection. This patient made a 50 per cent advance under dietary procedures, and finally made a complete symptomatic recovery by the continuation of these measures, supplemented by potassium iodid, sweats and cod liver oil.

Curve 5 (Jansen, Case 48) was afforded by a case of vertebral arthritis. The patient had had a tonsillectomy three months before,

and was making a substantial improvement in the absence of other demonstrable foci in the mouth or genito-urinary tract. This case was of much clinical interest (For details, see section on "Clinical Considerations")

Curve 6 (Lum, Case 13) is that of a woman, 42 years of age, studied by permission of the commanding officer, who had been exhaustively examined and treated for foci to the point of removing her appendix, and an operation for gallstones, which latter proved unnecessary. She was at this time suffering from a subacute arthritis<sup>21a</sup>. As a routine measure, and in the absence of any detectable pathology,

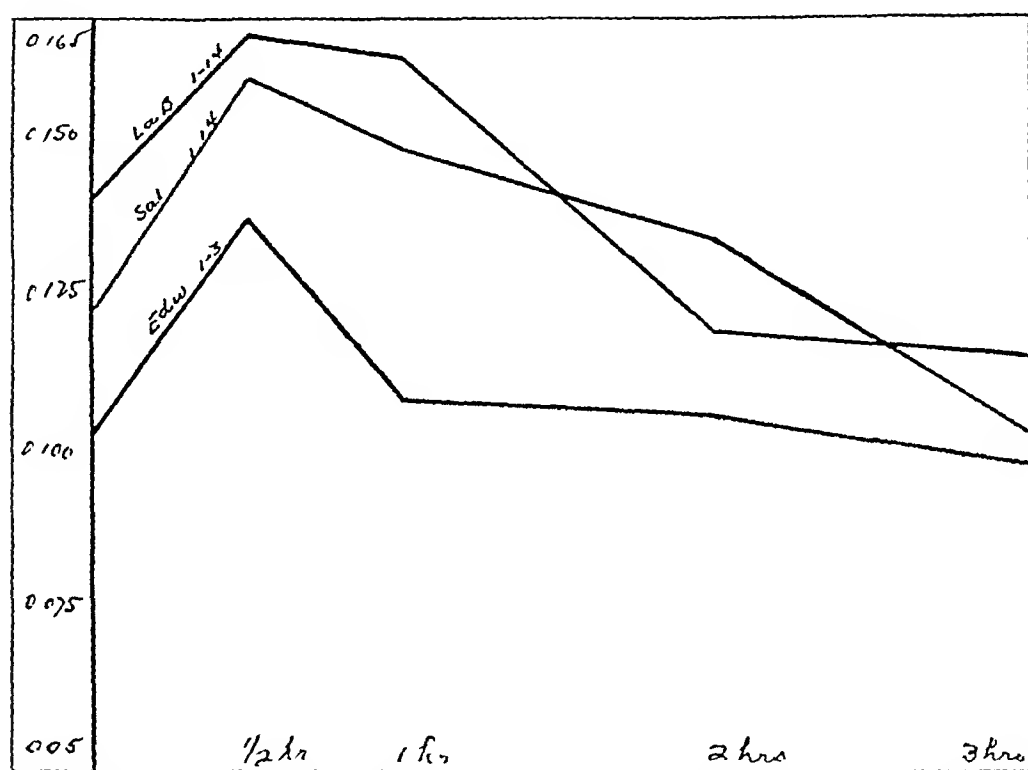


Chart 14—Normal and slightly lowered sugar tolerance in normal men with enlarged tonsils but no systemic symptoms

her tonsils were removed June, 1919. They proved negative for *Streptococcus hemolyticus*, were very small and were apparently not potential or actual foci of infection. She was still sick in February, 1920.

Case 57 (Langenberger) is another example of the same condition, not charted here, and others could be cited.

<sup>21a</sup> This patient kept her symptoms more or less modified by a low dietary, which she was led to adopt largely by her own experience. This diet was shown later to average about 2,000 calories. The beneficial effect of a very low diet or starvation on her symptoms had been repeatedly demonstrated and it is planned to report this case in greater detail later.

Chart 16 shows the curves obtained from three supposedly healthy persons, the subjects of marked tonsillar pathology without symptoms. One curve was very slightly elevated above the normal, and the other two fell within normal limits. One of these patients showed such gross pathology that his tonsils were removed a day or two later as a prophylactic measure. The significance of this chart is further borne out by the curves in the convalescent arthritics, three of whom were the subject of demonstrable surgical foci and yet showed a normal tolerance.

It is important, therefore, to note that, by and large, the disturbance of the sugar tolerance, as here considered, due to focal infection, apparently accompanies the failure of the organism successfully to maintain its wall of defense and is apparently restored to normal when this defense returns. In this light a lowered tolerance, following on a focus, becomes an intermediary, or, at least, a concomitant step in the pathology of arthritis and possibly other conditions as well.

In the course of conducting 109 complete sugar tolerance tests, a number of points developed which were of considerable interest, but could not be carried to their full development, partly because of the closure of the hospital and partly because of the press of other work. One of these occurred in connection with Case 22 (Oberg), described fully under "Dietary Considerations," the sugar tolerance at various times being graphically portrayed on Chart 12. This chart is drawn to a scale different from the others owing to the impossibility otherwise of including on it the uppermost curve.

In the course of the treatment of this soldier he was subjected to a sharp fast, amounting practically to starvation, which lasted during February 27, 28, and March 1, and until noon of March 2. On the morning of March 2, a sugar tolerance test was conducted. At that time he showed a moderate starvation acidosis, as indicated by acetone bodies in the blood plasma and urine, and a blood carbon dioxide of slightly under 50 volumes per cent. Reference to the chart shows that although the fasting blood sugar was at about the previous level, he showed a very marked intolerance to the ingested glucose, the curve rising to about 0.325 per cent at the end of the second hour, being still greatly elevated at the end of the third hour. One other case illustrative of the same phenomenon has come to our attention, and it appears that the condition of acidosis may be accompanied by a greatly lowered sugar tolerance, or may at least further depress an existing low tolerance. This point is worthy of further attention. March 14, when his acidosis had been relieved by feeding carbohydrate, the sugar tolerance fell markedly to a point distinctly lower than it had been at any time previously, the highest point on the curve being 0.198 per cent.

TABLE 15—SUGAR TOLERANCE FOR ARTHRITICS

Name	Date	Fasting		Half Hour		One Hour		Two Hour		Three Hour	
		Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma
Gekman	2/ 9	100	097	168	183	159	160	111	107	113	101
Moseley	2/ 9	095	097	111	113	107	100	084	079	083	079
Black	2/ 9	121	119	190	188	174	168	115	102	088	074
Stone	2/10	109	108	150		140	137	092	091	080	081
Collins	2/10	120		171		126	123	114	108	110	100
Stewart	2/10	103	099	188	193	135	139	097	095	102	096
	2/17		119		147		117		112		112
(after exercise)	2/18		150		230		210		165		
Cullen	2/12	100	097	182	197	135	131	140	080	080	075
	2/17		130		195		153		120		088
(after exercise)	2/18		119		143		248		197		
Moehler	2/11		125		138		131		079		110
Moon	2/11		114		148		124		091		100
Gaffney	2/12	110	107	152	150		122	097	081		097
Cabbage	2/12	113	107	143	144	131	125	088	083	088	098
Robbins	2/14	107	110	130	132	117	120	107	104	093	088
	2/18	118	115	169	167	120	115	118	114	110	102
Tally	2/19		120		125		133		090		107
Morris	2/19	110	106	144	144	117	115	101	099		
Thompson	2/19	115	120	100	108	133	130	088	082	092	087
Gross	2/20		121		126		115		119		109
Greenberg	2/20	128	120	145	150	155	156	100	100	100	100
Kerr	2/20	139	131	137	144	143	131	125	121	125	090
Clement	3/20			225	230						
Bruno	4/16	121	123	169	171	156	150				
(after exercise)	4/17	111	112	138	140	111	111				
Mean of all but those after exercise		115	114	154	154	140	135	110	106	100	095

TABLE 16—SUGAR TOLERANCE FOR OTHER PATHOLOGIC CONDITIONS

Name	Date	Fast-ing		Half Hour		One Hour		Two Hour		Three Hour	
		Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma
LaBovteaux	1/14	142		167		163		120		116	
Salvatore	1/14	124		160		149		134		103	
Meador	1/14	131		185		153		167		108	
Fountain	1/18	143		206		155		111		104	
Campbell	1/18	136		188		132		094		093	
Harris	1/18	107		150		171		116		075	
King	1/18	125		162		155		105		100	
Muse	1/23	147		234		185		172		153	
Fauts	1/26		121		152		121		108	098	
Frogley	2/ 6		136		147		158		123		
Smith	2/ 7	100	102	153	153	130	124	120	116	111	108
Hampton	3/21	100		125		129		108		084	
Mean of 10		124*	118	176	148	157	138	120	114	102	099

\* This figure for the fasting level of the whole blood is too high. The value for the plasma of the fasting blood is more nearly correct.



There is in this observation an apparent incompatibility between the relief of symptoms, accompanied eventually by a lowered sugar curve, following a reduced ingestion of carbohydrate, on the one hand, and the greatly heightened curve consequent upon complete starvation on the other hand. This discrepancy is more apparent than real, how-

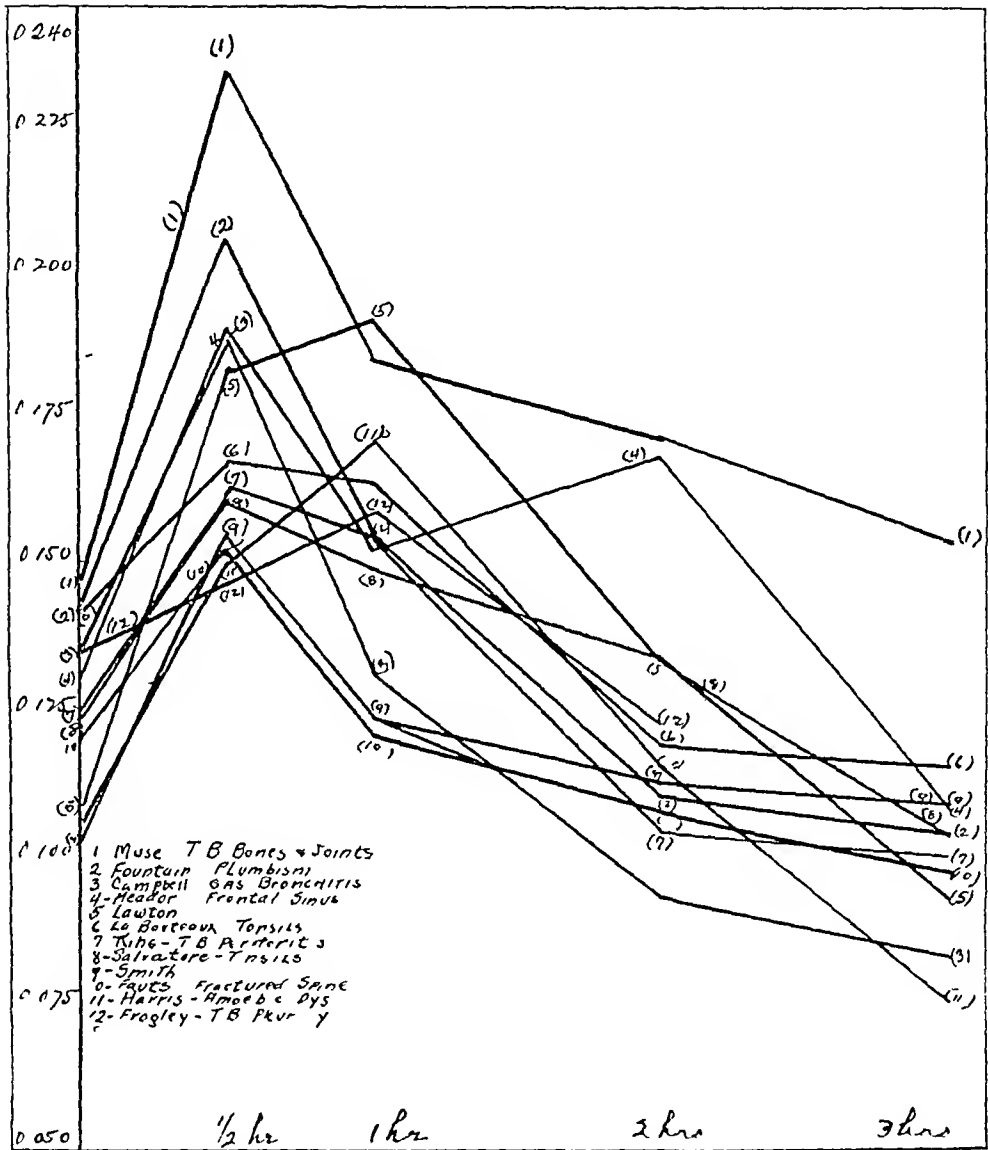


Chart 15—The sugar tolerance in miscellaneous pathologic cases

ever, as the condition of starvation induces an added pathology of its own and otherwise modifies normal physiologic processes <sup>21b</sup>

A lowered sugar tolerance is specific for no disease and has been noted in a variety of conditions. It has been regarded, however, as more or less peculiar to certain conditions and definitely characteristic

<sup>21b</sup> It is planned to discuss this point more fully at a later date

of some of them. It is important that there be recorded the results of sugar tolerance tests in as many different diseases as possible, and there were, therefore, included in the present study determinations of the sugar tolerance in twelve cases of miscellaneous diseases at large as they presented at the hospital.

Reference to Chart 15 will show the studies and the results of the test in each case. The highest curve is that afforded by a colored man, Case 18 (Muse), with widespread tuberculosis of the periosteum of the long bones, of the phalanges and of joints of the hands and feet. It is a moot point whether this case does not belong as much in the group of arthritics as elsewhere, since he also had secondary infection of the exposed and denuded bony surfaces.

The next highest curve is that in a case of chronic lead poisoning with the marked atrophy characteristic of that condition. The next highest curve was that of an officer alleged to have arthritis, accompanied by mild neurasthenia, and was accidentally included on this chart. It is rather noteworthy that Curve 7 and Curve 12 were afforded by cases of tuberculous peritonitis and tuberculous pleurisy, respectively, the former being only slightly elevated, and the latter well within normal limits. The case of tuberculous peritonitis was in a satisfactory condition of stability, but the case of pleurisy, in an army nurse, showed a large effusion in one pleural cavity. The diagnoses of the other conditions are noted on the curves.

Chart 16 is designed to illustrate the relative positions of the mean curves obtained from the various groups of cases studied. Reference to it shows that the severe arthritics gave the highest curves, the miscellaneous pathologic cases the next highest and moderate arthritics the next; the mild and convalescent arthritics followed with curves of about the same height, the curves in the normal cases being the lowest of all. It is to be noted that the miscellaneous pathologic cases were studied and recorded as they became available, and that the composite curve for them fell by chance in the position indicated. It is probable that selection could be made of certain types of miscellaneous pathologic cases which would determine such a composite curve at either a higher or a lower level according to the groups chosen.

It has generally been believed, as Hamman and Hirschman<sup>16</sup> point out, that, with the exception of disease of the pancreas, disturbances of the thyroid are the most common cause of altered carbohydrate tolerance. These authors emphasize, however, that even in hypothyroidism, sugar tolerance shows perplexing combinations, although in a general way low in hyperthyroidism, and abnormally high in hypothyroidism and that individual patients display wide latitude in their responses. The same conditions obtain in connection with disturbances

of the hypophysis, where similar individual discrepancies occur. Again, it has long been known that in nephritis the blood sugar is often unusually high. However, as Hamman and Hirschman remark "It is not always high, sometimes it is at the normal level, and why some cases have hyperglycemia and others have not, has never been satisfactorily explained."

It would seem, however, in the light of the evidence herewith adduced, that lowering of the sugar tolerance, as exemplified by the glucose tolerance test, rests, in part at least, on somewhat more fundamental pathologic processes than has hitherto been suspected. It seems to stand in some relation to inflammatory processes at large, and it appears from the data adduced herewith, that the incidence of an inflammatory process in a healthy person may induce a lowered sugar tolerance, that is a high curve<sup>22</sup>. There can be here instanced the case of Meador, a normal man, before and after the onset of frontal sinusitis. As seen by referring to Chart 2, illustrating the sugar tolerance of normal individuals, he there gave a curve (No 8, Dec 28, 1918), which rose only to 0.127 per cent at the end of the first hour, and later when he was the subject of an acute inflammatory process, he gave a curve<sup>23</sup> which was at 0.190 per cent at the end of one-half hour, at 0.152 per cent at the end of the first hour and at 0.167 per cent at the end of the second hour. On the other hand, other curves here adduced definitely prove that a lowered sugar tolerance of marked degree may abruptly return to normal after the removal of a focus of infection. This is illustrated in four cases of this series<sup>24</sup> in such a striking way as to be unquestionable.

It is entirely possible that some departures from normal observed in studying nephritis and thyroid and hypophyseal disorders, etc., are referable to such agencies as focal infections, and that we may really be determining under these circumstances the lowered tolerance due to them rather than to the disease primarily under consideration.

This applies, of course, to the miscellaneous diseases we have studied and recorded on Chart 15, and suggested the inexpediency of extending such observations unless carefully controlled. Thus the high curve (2) afforded by the case of plumbism, for example, may have been due to a focus which we did not at that time search for or suspect as having any bearing on the result.

It would seem important, therefore, in studying the carbohydrate tolerance of any disease in a given individual, to make sure that there is no focus in the field operating to alter the reaction to the glucose tolerance test.

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<sup>22</sup> A high level of blood sugar in furunculosis has been noted by Gettler and St. George, *J. A. M. A.* **71** 2033 (Dec 21) 1918.

<sup>23</sup> Chart 15, miscellaneous pathologic cases, Curve 4, Jan 4, 1919.

<sup>24</sup> Charts 7, 8, 11 and 12.

Finally, there is called prominently into the foreground the possibility that other diseases, of which a lowered sugar tolerance is a recognized symptom, may originally owe their characteristic feature of a lowered tolerance to such factors as causative agents

A lowered sugar tolerance, as measured by the glucose tolerance test, seems to be a more common occurrence than has been appreciated. In view of the demonstrated relation of focal infection to sugar tolerance, in view of the frequency of foci in arthritis and at large, in view of the frequency of arthritis as a disease and the frequency

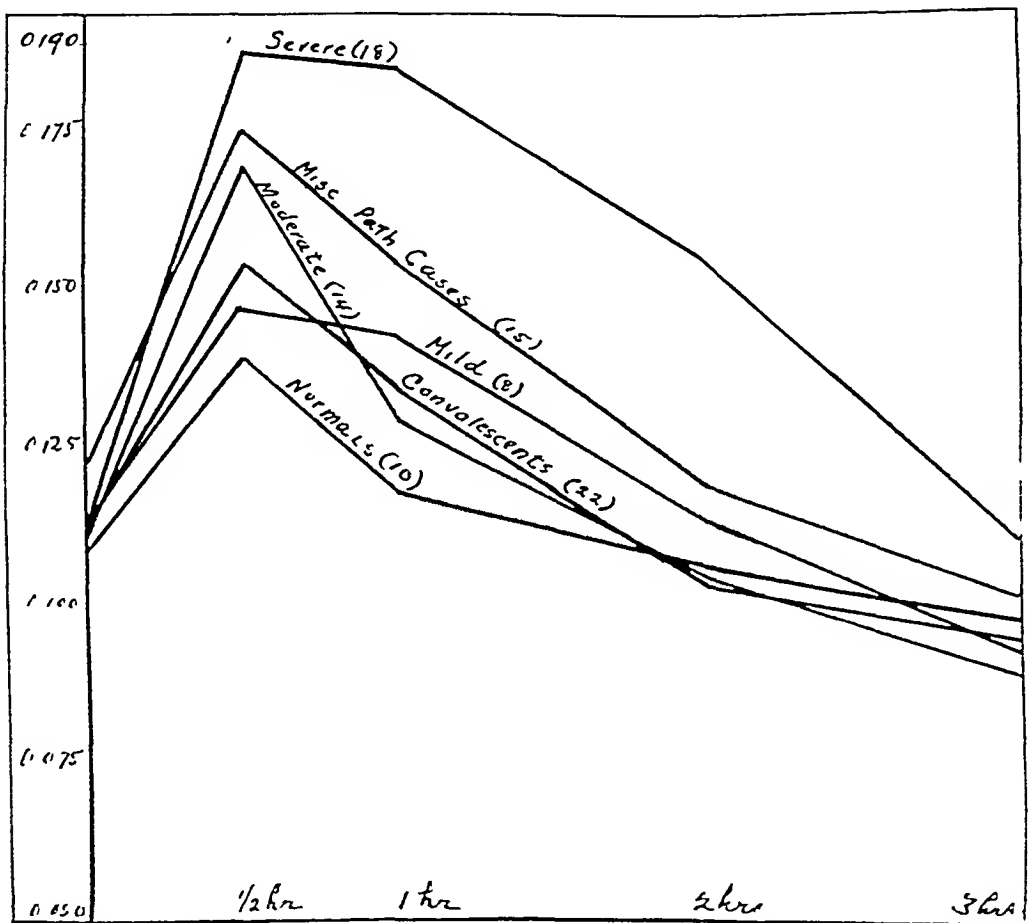


Chart 16—The average curves for the several groups of severe, moderate, mild and convalescent arthritics miscellaneous pathologic cases and normals

with which it is accompanied by a lowered sugar tolerance, it seems necessary to modify the view which ascribes to disturbance of thyroid function, next to disease of the pancreas, the most common cause of altered carbohydrate tolerance as measured by this test. The thyroid or other glands may be involved in the chain starting with focal infection but the glucose tolerance test reflects of course, only a part of the carbohydrate metabolism as a whole, and it is unprofitable in view of our incomplete knowledge to speculate much as to its full signifi-

cance It is clear, however, that most arthritic patients are unable to remove from the circulating blood, as does a normal individual, the carbohydrate which reaches it from the gastro-intestinal tract <sup>25</sup>

Hamman and Hirschman cite one case of rheumatic fever with afternoon temperature as high as 101 F, in which there only occurred a very slight rise of blood sugar after taking 100 gm of glucose Opportunity has permitted us to study only a few cases of febrile "inflammatory rheumatism," but the three cases which we observed showed a markedly lowered tolerance One of these has been recorded on Chart 11, giving two markedly elevated curves during the course of an acute febrile arthritis before and during symptomatic control of symptoms by acetylsalicylic acid Another case is illustrated on Chart 13 (Curve 2, Folden, Case 63) The patient was at that time apparently free from demonstrable surgical foci and was in the middle of a widespread rheumatic exacerbation This case is described under "Clinical Considerations" The third patient (McKensie, Case 62), during an attack of diffuse febrile arthritis with temperature up to 100.4 F at the time of the test, gave a lowered tolerance with a curve up to 0.215 per cent This curve is not charted, the figures for plasma sugar being 10 a m, 0.132 per cent fasting, 10.30 a m, 0.215 per cent after 100 gm glucose, 11 a m, 0.188 per cent This case was interesting in that the patient had had previous attacks of considerable severity, during which he received as many as eleven or twelve injections of phylacogens, one injection daily On admission from the command to the hospital, he had been sick and febrile for three days, and had had three injections of phylacogens, obtained on his own responsibility outside These were discontinued, and several days later the temperature fell to normal under routine treatment About ten days later, during a sick leave, he again became ill in the same way, being admitted with diffuse tenderness and fever He had had no phylacogens on this occasion It was at this time, April 29, 1919, that the above test was made This man had a dental abscess The tonsils and genito-urinary tract were reported normal, and he had a four plus Wassermann

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<sup>25</sup> The propriety of withholding large amounts of carbohydrate from some such cases finds ample corroboration in the restricted diets discussed in Part V It is suggested that this principle may also have application to some other conditions accompanied by this disturbance, in the effort to spare an obviously weakened function

# A METHOD OF ANALYZING THE ELECTRO-CARDIOGRAM<sup>1</sup>

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NEW YORK

The electrocardiogram as generally taken consists of three leads, obtained by using the two arms and the left leg as the contact or leading off points. Einthoven<sup>1</sup> has shown that these three leads bear a definite mathematical relationship to one another and has used an equilateral triangle to express this relationship graphically. For the better understanding of the succeeding parts of this paper we shall consider this mathematical relationship and its graphic representation at some length.

The mathematical relationship is expressed by the equation lead II equals lead III plus lead I. This means that the height of the ordinate in lead II of the electrocardiogram at any instant is the sum of the heights of the ordinates in leads III and I. The reason for this relationship can be appreciated if we consider the string galvanometer simply as an instrument for measuring differences of potential.<sup>2</sup> If now we wish to measure the difference of potential between the right arm and the left leg (lead II) at any instant, we can do it either directly by connecting the galvanometer with the right arm and left leg (lead II) or indirectly by taking some other point, as for example the left arm, finding the difference of potential between the right arm and the left arm (lead I) and between the left arm and the left leg (lead III) and adding them together. In a similar manner, if one wishes to find the difference in elevation (potential) between two towns, A and B, one may either subtract the elevation of A from the elevation of B (lead II), or one may take a third town, C, find the difference in elevation between A and C (lead I) and between B and C (lead III) and add them together. It is clear that the answer must be the same whichever way one proceeds. Thus, if the E K G gives us a true record of differences of potential, it must follow that for

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\* From the Cardiographic Laboratory of Mount Sinai Hospital, New York

1 Einthoven, W. The Different Forms of the Human Electrocardiogram and Their Signification, *Lancet* 1 853, 1912

2 The string galvanometer, because of the fact that the resistance of its circuit is not infinite, has a slight tendency to decrease the difference of potential between the leading off points, but ordinarily the error from this source is negligible, and the mathematical relationship between leads holds within the limits of experimental error

any and every moment during the cardiac cycle lead II equals lead III plus lead I, or, as it is more convenient for practical purposes to put it, lead II minus lead I equals lead III

To express this relation graphically Einthoven<sup>1, 3</sup> makes use of an equilateral triangle. The peculiar fitness of the equilateral triangle is due to the fact that the projections on the sides of an equilateral triangle of any straight line drawn within the triangle have a relationship similar to the relationship between the leads of an electrocardiogram. Figure 1 will demonstrate this point.

O A is any straight line drawn within the equilateral triangle R L F. The projections of O A on the three sides correspond to the three leads of the electrocardiogram and are labeled  $\epsilon_1$ ,  $\epsilon_2$  and  $\epsilon_3$ , respectively. The geometrical proof given shows that  $\epsilon_2 = \epsilon_3 + \epsilon_1$ . This equation will hold whatever be the position of O A, provided we give  $\epsilon_1$ ,  $\epsilon_2$  and  $\epsilon_3$  negative values when they would have negative values in the electrocardiogram.

Since Einthoven first demonstrated these mathematical and geometrical relationships, numerous investigators<sup>4</sup> have made use of them in analyzing electrocardiograms. The methods used have been various minor modifications of the original method of Einthoven, Fahr and de Waart,<sup>3</sup> which consists in finding the values of the three leads at any chosen instant and in substituting these values in certain formulas, thereby obtaining a linear value called "E" or the "manifest value," and an angular value, " $\alpha$ ." These two values determine the length and direction of a vector which corresponds to the line O A in Figure 1, O A in Einthoven's formula having the linear value E, and the angle C A O being  $\alpha$ . The length, E, of the vector gives the manifest value of the potential difference as shown by the three leads, but the vector as drawn by Einthoven in his original paper,<sup>1</sup> and thereafter by numerous users of this method<sup>3, 4</sup> is in a direction directly away from the point at which the center of negativity is located.

Carter, Richter and Greene<sup>5</sup> have developed an interesting modification of Einthoven's method. By means of an equilateral triangle,

3 Einthoven, W, Fahr, G, and deWaart, A. Ueber die Richtung und die manifeste Grosse der Potentialschwankungen im menschlichen Herzen und uber den Einfluss der Herzlage auf die Form des Elektrokardiogramms, *Arch f d ges Physiol* **150** 275, 1913.

4 Pardee, H E B. Form of the Electrocardiogram, *J A M A* **62** 1311 (April 25) 1914. Fahr, G. Simultaneous Records of Heart Sounds and the Electrocardiogram, *Heart* **4** 147, 1912.

5 Carter, E P, Richter, C P, and Greene, C H. A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Bull Johns Hopkins Hosp* **30** 162 (June) 1919.

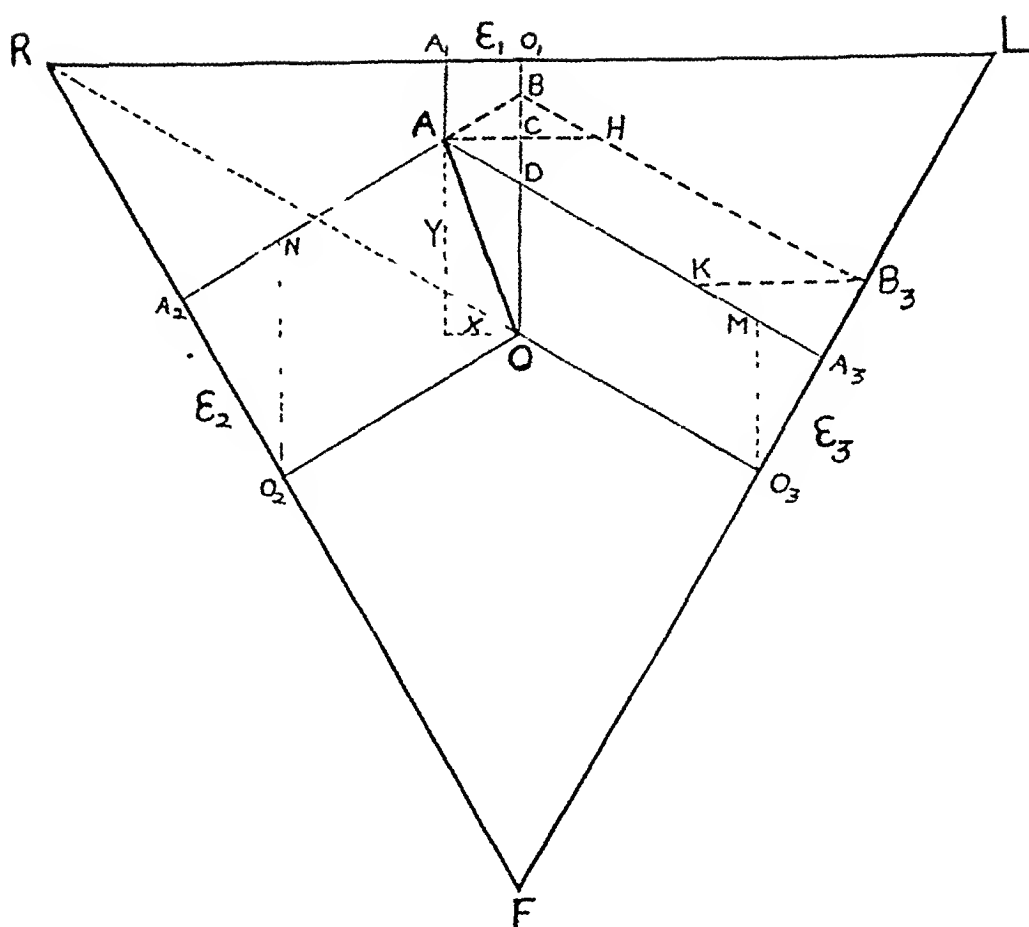


Fig 1—This is a simple geometrical demonstration of those properties which make the equilateral triangle peculiarly suitable for use in analysis of electrocardiograms

The values of the rectangular coordinates (X, Y) of a point (A) are found algebraically in terms of the three leads ( $\epsilon_1$ ,  $\epsilon_2$  and  $\epsilon_3$ )

**PROPOSITION** The longest projection on the sides of an equilateral triangle of any straight line drawn within an equilateral triangle equals the sum of the projections on the other two sides

**IFT** A O\* be any straight line drawn within the equilateral triangle R L F. Let  $\epsilon_1$ ,  $\epsilon_2$ , and  $\epsilon_3$  be the projections of A O on the three sides of the triangle, obtained by dropping perpendiculars ( $AA_1$ ,  $AA_2$ ,  $AA_3$ ,  $OO_1$ ,  $OO_2$ ,  $OO_3$ ) from the ends of the line A O upon the sides of the triangle

TO PROVE THAT  $\epsilon = \epsilon_2 + \epsilon_1$

- CONSTRUCTION**
- 1 Produce A A until it meets  $OO_1$  at B
  - 2 Draw  $BB_1$  perpendicular to L F
  - 3 Draw A H parallel to R L cutting B O at C
  - 4 Draw K B<sub>1</sub> parallel to A H
  - 5 Draw R O<sub>3</sub>\* the perpendicular bisector of L F

**PROOF**

$$\begin{aligned}
 A_2O_2 &= B_1O_1 && \text{for they are the projections of OB and the projections on the sides of an isosceles triangle of any line perpendicular to the base are equal} \\
 A_2O_2 &= A_3O_1 + A_1B_1 && \text{for } B_1O_1 = A_3O_1 + A_1B_1 \\
 \epsilon_2 &= \epsilon_3 + A_3B_1 && \text{for } A_2O_2 = \epsilon_2 \text{ and } A_3O_1 = \epsilon_3 \\
 &= \epsilon_3 + \frac{1}{2}KB_1 && \text{for } A_1B_1 = \frac{1}{2}KB_1 \text{ because triangle K A}_1\text{B}_1 \text{ is similar to triangle R L O}_1 \text{ and L O}_1 = \frac{1}{2} \text{ R L since } \angle \text{F L} = \angle \text{R L and L O}_1 = \frac{1}{2} \text{ F L} \\
 &= \epsilon_3 + \frac{1}{2}AH && \text{for } KB_1 = AH \text{ because parallel lines included between parallel lines are equal} \\
 &= \epsilon_3 + AC && \text{for } \frac{1}{2}AH = AC \text{ because } AC = CH \text{ since triangle A B C = triangle H B C (The two triangles have the common side B C, angle A C B = angle H C B = a right angle and angle A B C = angle H B C = } 60^\circ \text{ since perpendiculars to the sides of an equilateral triangle intersect at angles of } 60^\circ) \\
 \epsilon_2 &= \epsilon_3 + \epsilon_1 && \text{for } AC = \epsilon_1 \text{, because parallel lines included between parallel lines are equal}
 \end{aligned}$$

Q E D

\*In the figure the point O has been made the center of the triangle for the sake of simplicity in construction but the proof does not depend on this fact and will hold whatever be the position of the line O A. As a matter of fact the point O is taken at the center of the triangle in the subsequent part of this paper



TO FIND THE VALUE OF THE RECTANGULAR COORDINATES ( $\lambda$ ,  $Y$ ) OF THE POINT A IN TERMS OF  $\epsilon_1$ ,  $\epsilon_2$ , AND  $\epsilon_3$

Draw  $NO_2$  and  $MO_3$  parallel to  $OO_1$

Then  $X=A$   $C=A_1O_1=\epsilon_1$

$$Y=C O=(B O-B C)=(D O+D C)$$

$$=\frac{1}{2} (B O-B C+D O+D C)$$

$$=\frac{1}{2} (B O+D O) \quad \text{for } B C=D C \text{ because triangle } A B D \text{ is an equilateral triangle (having its three sides perpendicular to the sides of the equilateral triangle } R L F) \text{ and } A C \text{ is the perpendicular bisector (being parallel to } R L \text{ and therefore perpendicular to } B D)$$

$$\delta=\frac{1}{2} (N O_2+M O_3) \quad \text{for } B O=N O_2 \text{ and } D O=M O_3 \text{ because parallel lines included between parallel lines are equal}$$

$$=\frac{1}{2} \left( \epsilon_2 \frac{2}{\sqrt{3}} + \epsilon_3 \frac{2}{\sqrt{3}} \right) \quad \text{for angle } N O_2 A_2=30^\circ=\text{angle } M O_3 A_3 \text{ and the secant of } 30^\circ=\frac{2}{\sqrt{3}}$$

$$Y=\frac{\epsilon_2+\epsilon_3}{\sqrt{3}}$$

accurately drawn, with its center at the center of a graduated circle, they have evaluated  $E$  and the angle  $\alpha$  geometrically instead of algebraically. In practice, this method is considerably easier than the original method.

It will be evident to the student of mathematics that Einthoven and his followers have used what is known as the polar system of coordinates, designating as  $E$  and  $\alpha$  what the mathematician ordinarily calls  $\rho$  and  $\theta$ . In July, 1916, after perusing H. B. Williams' paper,<sup>6</sup> I was led to investigate the properties of Einthoven's triangle and its application to electrocardiography. In this investigation a system of rectangular coordinates was employed, and the results have been so interesting and suggestive that it seems advisable to publish this method of analysis as a preliminary to the publication of the results that we have obtained by its use.

The basic principle of the method can be demonstrated by means of Figure 1. Instead of finding values  $E$  and  $\alpha$  which correspond to  $\rho$  and  $\theta$  in the polar system of coordinates, we have found two values which correspond to what are known as  $X$  and  $Y$  in the rectangular system of coordinates. These two values locate the point  $A$ , and, since the point  $O$  is fixed at the center of the triangle,<sup>7</sup> give us the same information that was given by  $E$  and the angle  $\alpha$ .

But, although our values for  $X$  and  $Y$  give us the same information that was given by  $E$  and  $\alpha$ , they give it in a much more useful form. In the first place, it is easier to visualize points located by rectangular than by polar coordinates. It is simpler to think of a point with the value  $X=4$ ,  $Y=3$  than it is to think of the same point with the value  $\rho=5$ ,  $\theta=37^\circ$ , or  $E=5$ ,  $\alpha=37^\circ$ . Again, it is simpler to chart a point

<sup>6</sup> Williams, H. B. On the Cause of the Phase Difference Frequently Observed Between Homonymous Peaks of the Electrocardiogram, *Am J Physiol* **35** 292 (Oct.) 1914.

<sup>7</sup> See footnote to Figure 1.

located by rectangular coordinates than the same point located by polar coordinates. Ordinary cross section paper can be used, and there is little possibility of error. Furthermore, the mathematics involved in locating a point are simpler with rectangular coordinates, viz

rectangular coordinates<sup>8</sup>

$$X = \epsilon_1$$

$$Y = \frac{\epsilon_2 + \epsilon_3}{\sqrt{3}}$$

polar coordinates<sup>9</sup>

$$a = \tan^{-1} \frac{2\epsilon_2 - \epsilon_1}{\epsilon_1 \sqrt{3}}$$

$$E = \frac{\epsilon_1}{\cos a}$$

But the greatest advantage to be obtained by the use of rectangular coordinates is due to the fact that it is comparatively easy with this system to plot consecutively the successive values of X and Y through a complete cardiac cycle and to connect these consecutive points with a fairly smooth curve which we shall call the "monocardiogram," for reasons which will appear later.

In order to understand the significance of this "monocardiogram," we shall revert for a moment to Einthoven's original discussion of the equilateral triangle. Einthoven,<sup>9</sup> speaking of the Q R S wave of the electrocardiogram, says "The curve must represent, under all circumstances and in every moment the algebraic sum of all the potential differences which at that moment are developed in the heart." We shall try to express the same thought by saying that the point X, Y (A in Figure 1), which we locate by our system of coordinates, represents the "center of negativity" of the heart at that instant, meaning by "center of negativity" a point somewhat analogous to "center of gravity" and "center of mass." If at any moment there are present in the heart several (negative) electrical charges which have value (intensity, voltage) and position (direction) then the center of negativity is that point which represents the algebraic sum of all the potential differences. The line, E, in Einthoven's drawings, which connects this point with the center of the equilateral triangle will, by its projections on the three sides of the triangle, give the values of the galvanometer deflections (ordinates) for the three leads at that particular instant. By finding the location of the center of negativity at consecutive instants, and connecting the points thus found by a continuous line, we obtain a curve which represents the successive algebraic sums of the potential differences that develop in the heart during the cardiac cycle. This curve we have called the monocardiogram to distinguish it from the ordinary electrocardiogram, which is really a "triacardiogram" or a threefold derivative of the monocardiogram.

<sup>8</sup> See Figure 1

<sup>9</sup> Lancet **1** 856, 1912

The monocardioqram is really a fusion of the three leads of the electrocardiogram into a single curve by an algebraic reversal of the process by which three leads are obtained from one heart. Its study brings us much nearer the real electrical events of the cardiac cycle than does the study of the ordinary E K G, or tricardiogram which is derived from it by our present method of leading off. Figure 2 illustrates this fact. It shows the monocardioqram of the Q R S deflection taken from an electrocardiogram published by Einthoven (Fig 8)<sup>1</sup> and used by Einthoven as a demonstration in his original description of

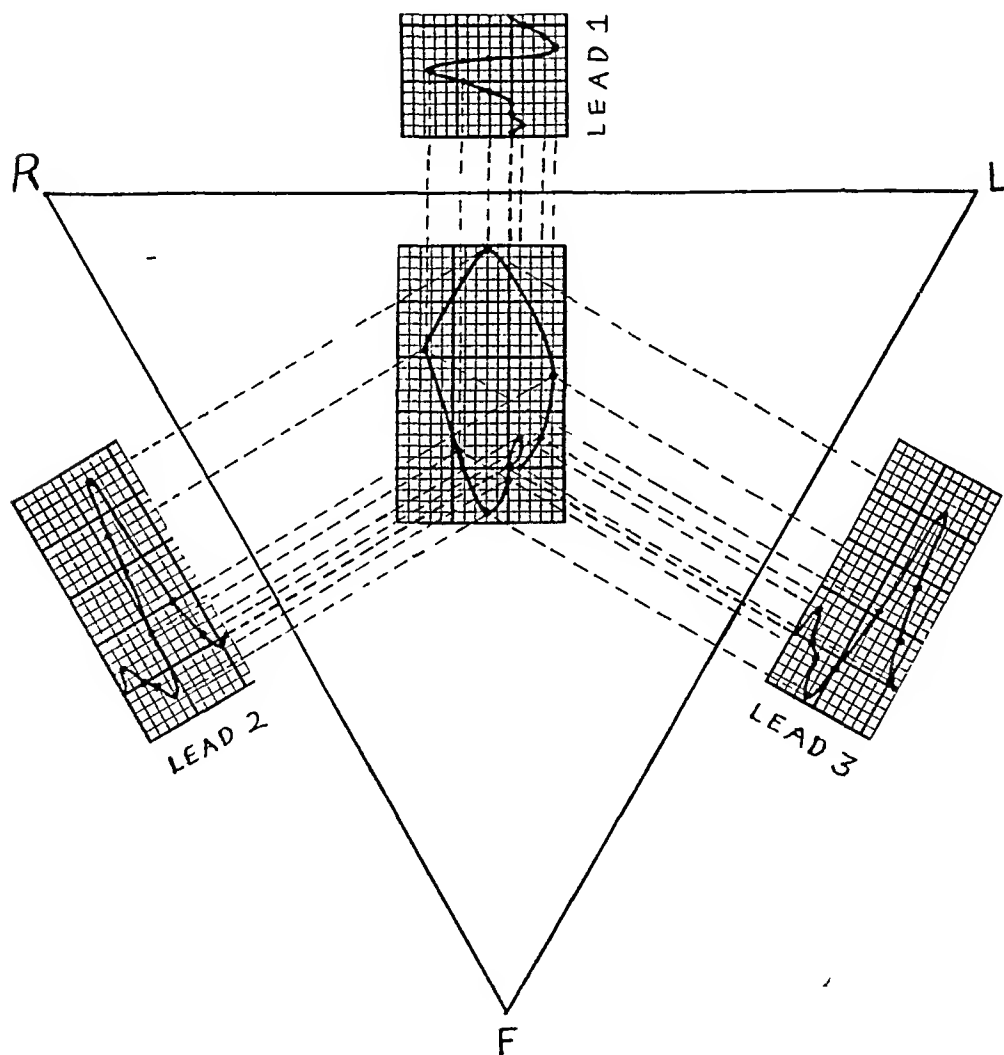


Fig 2—This figure shows the monocardioqram which is derived from an electrocardiogram published by Einthoven (Fig 8)<sup>1</sup>. It can be seen that the three leads of the electrocardiogram are really derivatives of the monocardioqram, obtained by successive projections of the monocardioqram on the three sides of the equilateral triangle.

Note that in this monocardioqram, as in all the others shown in this article, the right side is on the observer's left. This is in accordance with ordinary cardiographic usage as regards Einthoven's triangle and facilitates interpretation.

the equilateral triangle. It can be seen that leads I, II and III are really derivatives obtained by successive projections of a vector connecting the center of our triangle with the successive positions of the center of negativity. Thus the monocardioqram represents as nearly as can be represented in a plane figure, the actual electrical events of a cardiac cycle.

The direction and shape of the monocardioqram have an anatomic significance which is indicated only obscurely by the direction and shape of the ordinary electrocardioqram. The shape of the ordinary E K G may be considered the result of the projection of the monocardioqram (M C G) on the sides of an equilateral triangle, and thus the anatomic significance becomes distorted and obscured, but the M C G itself owes its shape to the actual electrical events of the cardiac cycle and shows the successive relative positions of the center of negativity. Thus, it affords us a method of localizing, in a plane, various parts of the cardiac musculature, of analyzing an E K G with regard to its anatomic significance, of determining what part of the cardiac musculature is responsible for various types of bizarre and abnormal E K G's, and of locating the site of origin of extrasystoles. By means of three leads taken in a horizontal plane and similarly analyzed we can obtain a "transverse monocardioqram" and get a three dimensional view of events during the cardiac cycle. It is our intention in further communications to discuss the points just mentioned and more especially to use the monocardioqram for the analysis of E K G's in which it is assumed that there are defects in various localized regions of the cardiac musculature, i. e., in cases of sub-endocardial myocarditis as described by Oppenheimer and Rothschild<sup>10</sup>.

For the application of our method to the analysis of an electrocardioqram it is not absolutely necessary to have simultaneous E K G's of the several leads. Provided the string has been carefully standardized it is quite practicable to proceed as follows:

- 1 By means of a camera lucida drawing, photographic enlargement, or by examination of the film with a microscope a series of careful measurements of a complete heart cycle is made for each lead. If there is evidence of respiratory or sinus arrhythmia care must be taken to select cycles which are in the same phase. The values of the ordinates are measured in millimeters for every hundredth of a second or less.

- 2 By the method of trial and error the three series of measurements are so arranged that for every moment during the cardiac cycle

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<sup>10</sup> Oppenheimer, B. S., and Rothschild, M. A. Electrocardiographic Changes Associated with Myocardial Involvement, *J. A. M. A.* **69**:429 (Aug 11) 1917.

lead II minus lead I equals lead III In most curves, especially those with high peaks, this is a fairly easy matter

3 The value for X for each moment (0.01 second) is known, for it is the value of lead I (Fig 1), but the value of Y must be calculated as follows divide the algebraic sum of leads II and III by the square root of 3 This is done by means of Table 1, and gives us the successive value of Y

4 The successive positions of the point X, Y are plotted and connected with a fairly smooth curve, thus giving the monocardio gram

Figure 3 illustrates the method of procedure The camera lucida enlargement of the E K G is shown, the values of the three leads for every hundredth of a second are shown properly arranged, the values of Y are shown calculated, and the monocardio gram resulting is shown

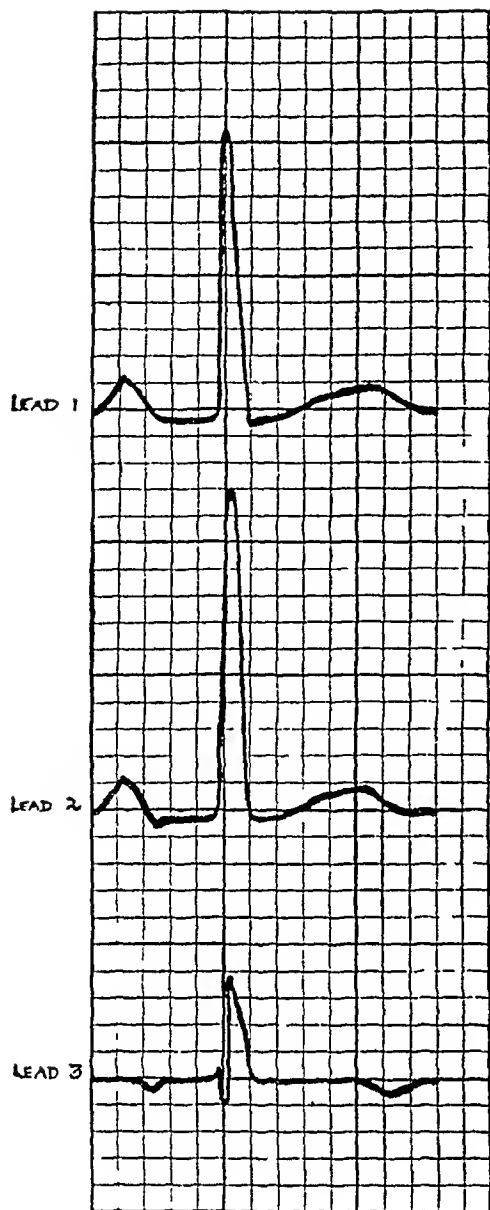
Table 1—This table is used for the calculation of the value  $Y \left( \frac{\epsilon_2 + \epsilon_3}{\sqrt{3}} \right)$  It is used like a logarithm table For example at the instant labelled 20 in the table in Figure 3, the ordinate in lead II measured 97 mm, and the ordinate in lead III measured —8 mm The algebraic sum of 97 and —8 is 89 If we look this number up in our table we use the horizontal row labelled 8 and the vertical row labelled 9 The number which we find at the intersection of these two rows is 5138 and thus our value for Y is approximately 51 The values for Y at other instants were found in the same manner by adding the values of leads II and III and using the table to simplify the process of dividing by  $\sqrt{3}$

$\sqrt{3} = 1.7320+$

$\frac{\epsilon_2 + \epsilon_3}{\sqrt{3}}$	0	1	2	3	4	5	6	7	8	9	Differ ences
0		0 0577	0 1155	0 1732	0 2309	0 2887	0 3464	0 4041	0 4619	0 5196	
1	0 57735	0 6351	0 6928	0 7506	0 8083	0 8660	0 9238	0 9815	1 039	1 097	1 0 00577
2	1 1547	1 212	1 270	1 328	1 386	1 443	1 501	1 559	1 617	1 674	2 0 01155
3	1 7321	1 790	1 848	1 905	1 963	2 021	2 079	2 136	2 194	2 252	3 0 01732
4	2 3094	2 367	2 425	2 483	2 540	2 598	2 656	2 714	2 771	2 829	4 0 02309
5	2 8868	2 944	3 002	3 060	3 118	3 175	3 233	3 291	3 349	3 406	5 0 02887
6	3 4641	3 522	3 580	3 637	3 695	3 753	3 811	3 868	3 926	3 984	6 0 03464
7	4 0415	4 099	4 157	4 215	4 272	4 330	4 388	4 446	4 503	4 561	7 0 04041
8	4 6188	4 677	4 734	4 792	4 850	4 907	4 965	5 023	5 081	5 138	8 0 04619
9	5 1962	5 254	5 312	5 369	5 427	5 485	5 543	5 600	5 658	5 716	9 0 05196

The use of simultaneous electrocardiograms is theoretically desirable, but we are not confined to such simultaneous records in the employment of this method Successive heart cycles in an individual are so nearly alike that, provided proper precautions are exercised in the choice of cycles, the rule, lead II minus lead I equals lead III, holds for practical purposes In practice we have found it possible to apply this method of analysis to the ordinary E K G as usually taken

Figure 4 shows a monocardio gram derived from one of the rare electrocardiograms in which all three leads were taken simultaneously The original E K G was published by Einthoven, Bergansius and



	X			Y
	Lead 1	Lead 2	Lead 3	$\frac{2+3}{\sqrt{3}}$
0	0	0	0	0
1	0.1	0.1	0	0.06
2	0.4	0.4	0	0.2
3	0.7	0.7	0	0.4
4	1.0	1.0	0	0.6
5	1.3	1.3	0	0.75
6	1.0	1.0	0	0.6
7	0.8	0.8	0	0.46
8	0.5	0.4	-0.1	0.17
9	0.1	-0.2	-0.3	-0.3
10	-0.3	-0.4	-0.1	-0.3
11	-0.3	-0.3	0	-0.17
12	-0.3	-0.3	0	-0.17
13	-0.3	-0.3	0	-0.17
14	-0.3	-0.3	0	-0.17
15	-0.3	-0.3	0	-0.17
16	-0.3	-0.3	0	-0.17
17	-0.3	-0.3	0	-0.17
18	-0.3	-0.3	0	-0.17
19	0	0.4	0.4	0.46
20	10.5	9.7	-0.8	5.1
21	8.2	12.0	3.8	9.3
22	5	8	3	6.4
23	0	2	2	2.3
24	-0.5	-0.2	0.3	0.06
25	-0.3	-0.3	0	-0.17
26	-0.3	-0.3	0	-0.17
27	-0.3	-0.3	0	-0.17
28	-0.2	-0.2	0	-0.1
29	-0.1	-0.1	0	-0.06
30	0	0	0	0
31	0.1	0.1	0	0.06
32	0.2	0.2	0	0.1
33	0.4	0.4	0	0.2
34	0.5	0.5	0	0.3
35	0.6	0.6	0	0.35
36	0.7	0.7	0	0.4
37	0.7	0.7	0	0.4
38	0.8	0.8	0	0.46
39	0.8	0.8	0	0.46
40	0.9	0.9	0	0.5
41	0.9	0.9	0	0.5
42	0.9	0.8	-0.1	0.4
43	0.9	0.6	-0.3	0.17
44	0.8	0.3	-0.5	-0.1
45	0.7	0.2	-0.5	-0.17
46	0.5	0.1	-0.4	-0.17
47	0.3	0	-0.3	-0.17
48	0.2	0	-0.2	-0.1
49	0.1	0	-0.1	-0.06
50	0	0	0	0

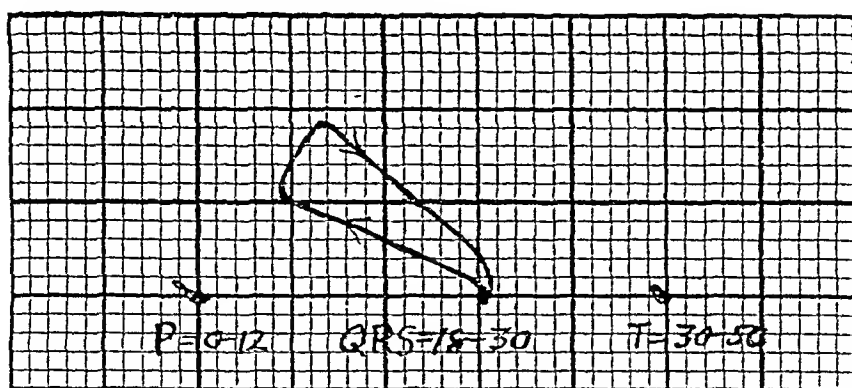


Fig 3—This figure shows the method of obtaining a monocardigram. Above, to the left, is shown a camera lucida drawing of the three leads of an electrocardiogram. The ordinates represent 0.04 second and the abscissae represent 0.1 millivolt. To the right is shown a table of values of the ordinates of the three leads for every 0.01 second properly arranged so that lead II minus lead I equals lead III for every instant. The fourth column of figures in the table gives the values of Y calculated by means of Table 1. Below is shown the monocardigram plotted by connecting successive values of the point, X, Y, with a smooth curve. The P, QRS, and T deflections are plotted separately. Positive values of X are plotted to the observer's left, for this is taken as the right side. Positive values of Y are plotted above the line, as is usual.

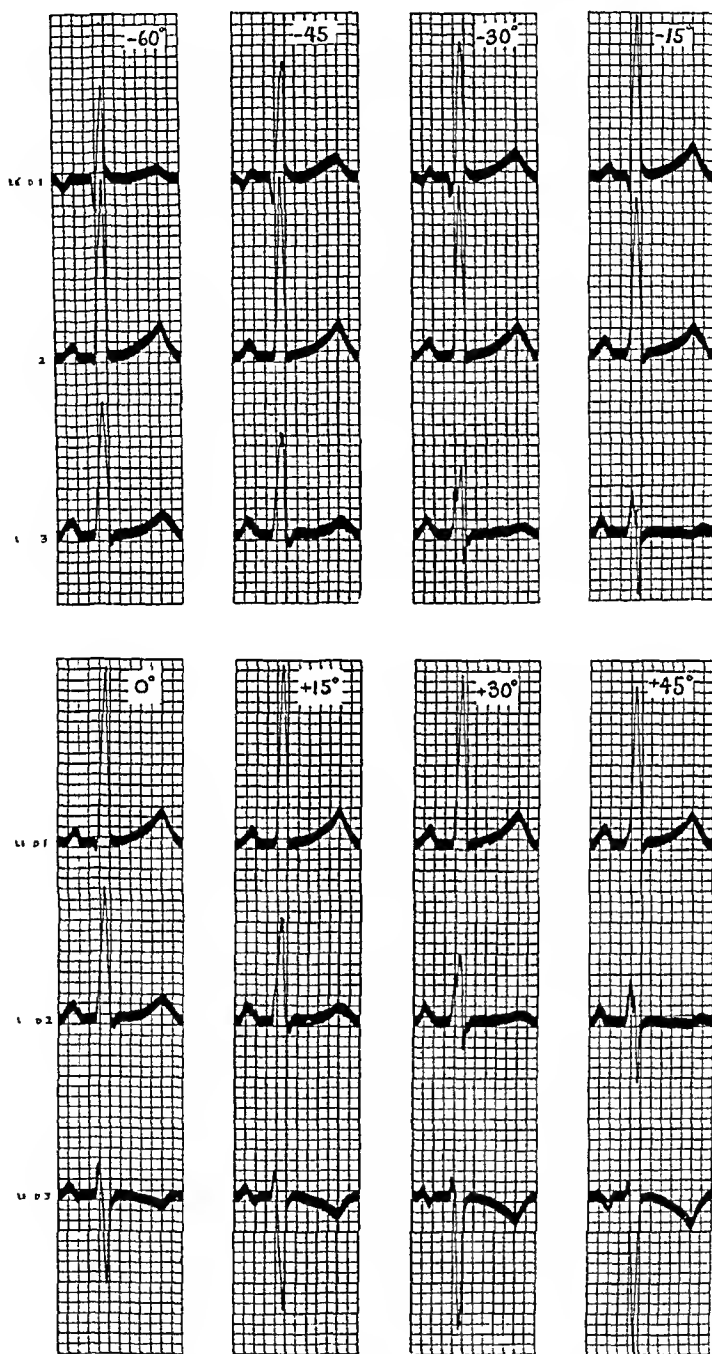
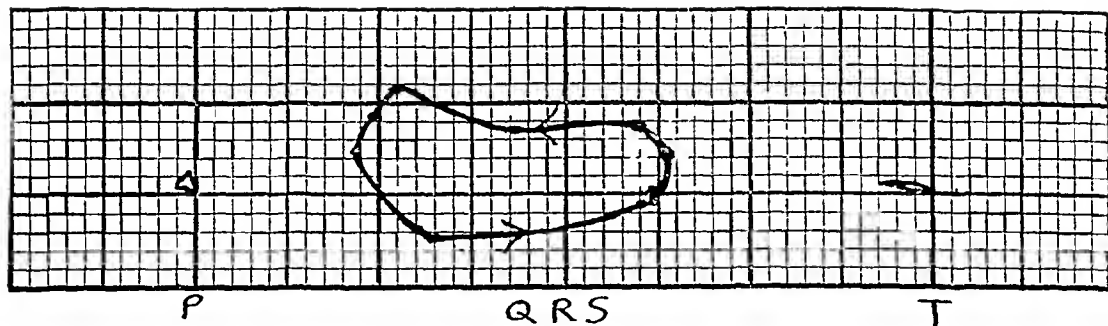


Fig 4—This shows the monophasic monophasic derived from an electrocardiogram published by Einthoven, Bergansius, and Bijtel<sup>11</sup> (Fig 3, Cycle 2) From this EKG (which is one of the very rare published electrocardiograms taken simultaneously in all three leads by means of three galvanometers) we have derived the monophasic, shown above Below the monophasic are shown eight pairs of derived electrocardiograms These were derived from the monophasic by a method similar to that illustrated in Figure 2 and they show the effect that rotation of the heart's axis would have on the electrocardiogram We have followed customary trigometrical notation and called clockwise rotation negative and counterclockwise rotation positive Thus by  $+30^\circ$  we mean that the heart is so rotated that the apex approaches the patient's left shoulder

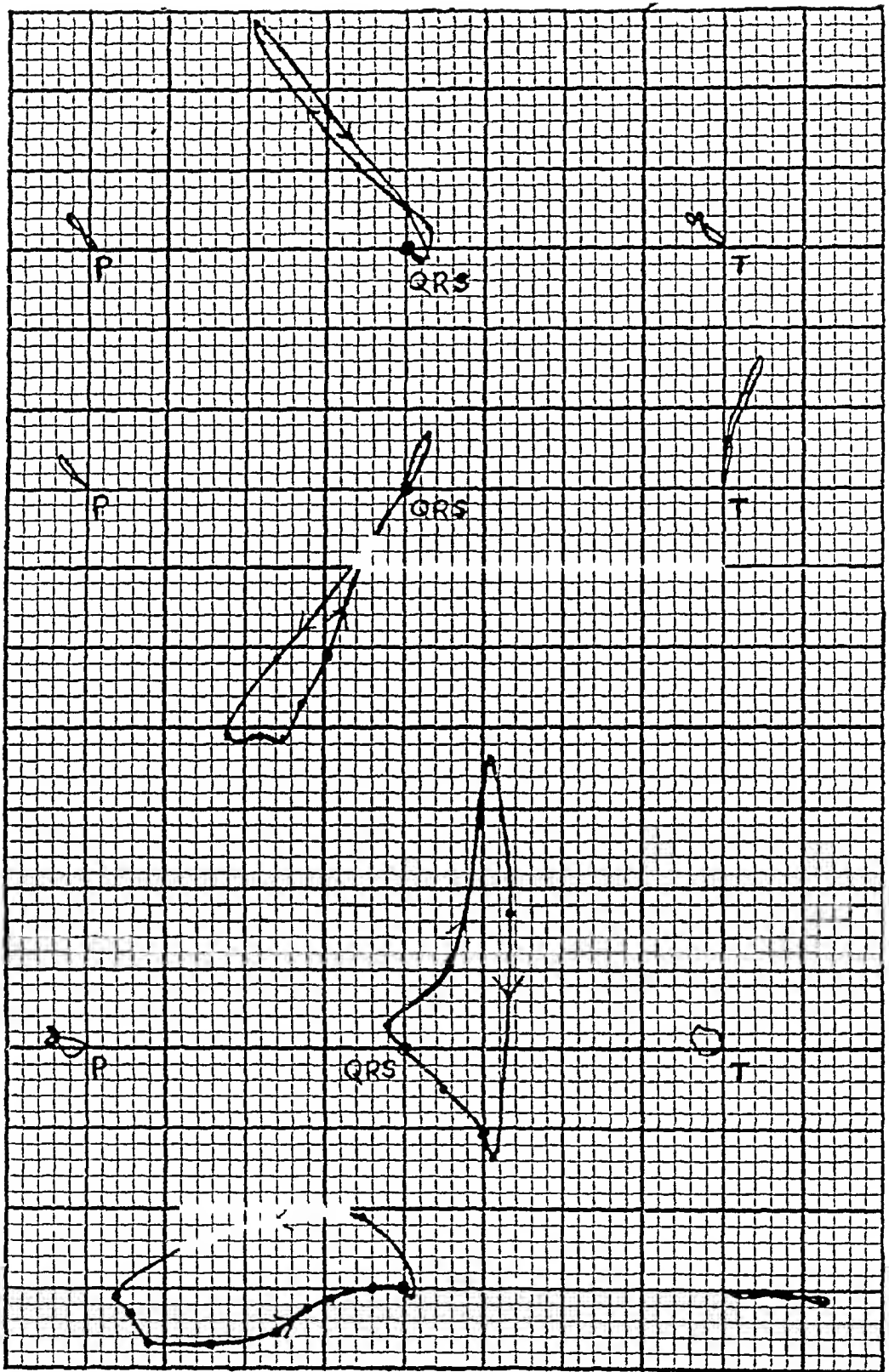


Fig 5—The uppermost monocardium is that of a normal heart. The second monocardium was derived from an E.K.G. which showed a characteristic *left ventricular preponderance* (main deflection upright in lead I and inverted in lead III).

The third monocardium was derived from an E.K.G. which showed a characteristic *right ventricular preponderance*.

The lowermost monocardium was derived from the electrocardiogram of a ventricular extrasystole. It points definitely to the right ventricle (observer's left).



Bijtel<sup>11</sup> Our figure shows a series of derived E K G's which demonstrate the effect that rotation of the heart's axis would have on the ordinary electrocardiogram. The series of E K G's was obtained by rotating the monocardigram and plotting the various resulting E K G's by a method similar to that illustrated in Figure 2. In Figure 2 the M C G is derived from the E K G. By reversing our procedure, we can plot the E K G from the M C G. By taking the M C G and rotating it 15 degrees we can plot out the E K G that would result if the heart itself were rotated 15 degrees. In this way we can obtain a series of E K G's that will show the effect of rotation of the heart's axis on the normal E K G. During normal respiration changes occur in the E K G which are probably due to a combination of rotation of the heart's axis and nervous effects.<sup>3</sup>

Monocardigrams of a normal heart, of left ventricular preponderance, of right ventricular preponderance, and of a ventricular extrasystole are shown in Figure 5. It is interesting to note that in ventricular preponderance, the preponderant or thickened ventricle shows a tardiness in electrical response which causes a shifting of the center of negativity to the side opposite the preponderant ventricle and thus gives E K G's which are characteristic of preponderance. It can be seen that the different electrocardiograms which are characteristic of various types of cardiac abnormality give monocardigrams of every different form. The anatomical significance of the monocardigram gives us reason to hope that this method of analysis will lead to closer correlation between cardiographic and pathologic findings.

#### SUMMARY

1 A new method is presented by which the ordinary three leads of the electrocardiogram are combined in a single curve, the monocardigram.

2 Usefulness of this method of analyzing the electrocardiogram is explained.

The writer wishes to acknowledge indebtedness to Dr. B. S. Oppenheimer for his assistance in the final preparation of this paper.

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11 Einthoven, W., Bergansius, F. L., and Bijtel, J. Die gleichzeitige Registrierung elektrischer Erscheinungen mittels zwei oder mehr Galvanometer und ihre Anwendung auf die Elektrokardiographie, *Arch f d ges Physiol* **164** 167, 1916.

# IRRITATION OF THE VAGUS AND HEMORRHAGIC EROSIONS OF THE STOMACH

KNUD NICOLAYSEN, M D

The so-called vegetative or autonomous peripheral nervous system, which consists of the vagus and the sympathetic, has been subjected to systematic investigation only recently. While numerous contributions have been made to the knowledge of the functions of this system, we are yet far from a clear understanding of its structure and mode of action. The ideas of Eppinger and Hess<sup>1</sup> concerning vagotony and sympathicotony are well known, but a few points may be discussed. We know that the vegetative nervous system consists of the vagus and the sympathetic, that they are antagonistic in most cases, holding each other normally in equilibrium, and that there are a number of substances which act as irritants or as paralyzers of these nerves. Thus pilocarpin irritates, atropin paralyzes the vagus, while epinephrin irritates the sympathetic, definite sympathetic paralyzers not being known. The antagonistic relation between the sympathetic and the vagus results, generally speaking, in that paralysis of the sympathetic produces the same symptoms as irritation of the vagus and vice versa. It also appears as if disturbed correlation between the endocrine organs may cause diminished or increased tonus in the vagus or sympathetic, or both. The vagus is the secretory and motor nerve of the stomach, hypersecretion, hyperchlorhydria and pyloric spasms are believed to result from irritation of the vagus and to be symptoms of vagotony. The similarity of these symptoms with those of ulcer of the stomach has led to the belief by some that ulcer also is associated with a vagotonic condition. Petrin and Thorling examined eighteen patients with ulcer of the stomach as to their reaction to pilocarpin and atropin, on the one hand, and epinephrin on the other, and came to the conclusion that a pronounced vagotony is often present in patients with ulcer, whereas a definite sympathicotony was observed only rarely, five of the patients reacting to atropin-pilocarpin as well as to epinephrin.

During recent years, a number of experimental investigations have been made in regard to the influence of the vegetative nervous system on the stomach, especially with respect to hemorrhages and erosions

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\* From the Pathologic-Anatomic Institute of the Rikshospital, Christiania.

1 Eppinger, H. and Hess, Leo. Zur Pathologie des vegetativen Nervensystems, *Ztschr f klin Med* 67 345, 1909, 68 205, 231 1909.

2 Petrin, K. and Thorling, I. Untersuchungen über das Vorkommen von Vagotonus und Sympathikotonus *Ztschr f klin Med* 73 27, 1911.

Finzi<sup>3</sup> removed one or both suprarenals in rabbits and dogs, and subsequently observed edema and hemorrhages in the gastric mucosa, degeneration of the epithelial cells, and even real ulceration, the greater the amount of suprarenal removed the more extensive the changes. After total extirpation, the animals lived only a few hours, but in some instances, in which a remnant of the suprarenal was left, the animals lived from fifty to sixty days. The changes in the gastric mucosa developed rapidly, but healed slowly with only slight tendency to scar formation. If epinephrin was given after the extirpation, changes in the stomach did not take place. In five cases of gastric and duodenal ulcer in man, he found changes in the suprarenal after death—thickening of the capsule, fatty changes and hemorrhages.

Friedman<sup>4</sup> observed erosions in the duodenum in dogs after repeated injections of epinephrin. He found that extirpation of one or both suprarenals, of one suprarenal and a lobe of the thyroid, or of a thyroid lobe alone, in dogs and rabbits, was followed by hemorrhages and erosions in the stomach except when the operation involved the suprarenals and the thyroid at the same time. Consequently, he concludes that the lesions in the mucosa of the stomach in suprarenal insufficiency are dependent on the integrity of the thyroid.

Mann<sup>5</sup> experimented on dogs and cats, removing both suprarenals in one or two sittings, and keeping the animals etherized until they died, usually from two to eight hours after the operations, but no ulcers resulted, removal of one suprarenal was followed by death in from five to 235 days, but no ulcers were found, except in one case, removal of both suprarenals in one or two sittings resulted in ulcers in the stomach or duodenum in 90 per cent. Mann holds that the ulcers developed as the animals became moribund. He saw two types, one superficial and diffuse—erosions—and the other a sharply defined ulcer.

Friedman reports that he was able to produce erosions in the stomach in three of four rabbits by injection of thyroid substance. Believing that these erosions were caused by vagotony due to hormones in the thyroid, he tried to cause vagotony in rabbits by injecting pilocarpin, and in the thirteen animals experimented on erosions were found in all in the stomach at the same time as salivation, diarrhea and increased secretion of bronchial mucus and of tears resulted. In nine animals injected alternately with pilocarpin and epinephrin, eight developed erosions in the stomach and the duodenum. He concludes

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3 Finzi, Otello. Ueber Veränderungen der Magenschleimhaut bei Tieren nach Nebennierenextirpation, *Virchows Arch f path Anat* **214** 413, 1913.

4 Friedman, G. A. Experimental Production of Lesions, Erosions and Acute Ulcers in Rabbits by Repeated Injections of Pilocarpin and Adrenalin, *J M Res* **38** 449, 1918, **32**.

5 Mann, Frank C. A Study of the Gastric Ulcer Following Removal of the Adrenals, *J Exper M* **23** 203, 1916.

that epinephrin, together with pilocarpin, acts particularly on the duodenal mucosa, while pilocarpin alone acts on the gastric mucosa. He allowed the animals to live only a few hours after the last injections of pilocarpin, and it is noteworthy that the erosions appeared very promptly.

The results discussed in the foregoing are of interest not only with respect to the actions of the vegetative nervous system and its relation to the endocrine organs, but also because they throw a new light on the genesis of hemorrhagic erosion and perhaps also of gastric and duodenal ulcer.

That irritation ("stimulation of the vagus or paralysis of the sympathetic") may cause changes in the lining of the stomach in animals has been established. The nature of these changes and their fate, as well as the histologic processes initiated, are, however, less clearly understood. It is these questions which I have studied in rabbits injected subcutaneously with 5 per cent pilocarpin hydrochlorate.

In all, twenty-five animals were used. The stomach was examined in all cases after formol fixation, the sections were stained with hematoxylin and eosin, van Gieson's method and Gram's method. Jenner's stain as recommended by Heyrovsky<sup>6</sup> was also used. The experiments are not described in order but in groups, and the same animals may be considered under more than one group.

Of ten animals which received from 10 to 35 cg pilocarpin in two or more injections of 5 cg each, and all of which died or were killed within twenty-four hours, nine showed changes in the lining of the stomach, three had in addition erosions or ulcers in the duodenum, only one animal being free from changes after twenty-four hours. This animal reacted to the injections with only slight salivation, whereas all the other animals immediately after the injection presented salivation, lacrimation, diarrhea and rapid respiration. Each animal, however, did not react in proportion to the amount of pilocarpin injected, and animals receiving the same amount of pilocarpin reacted in different degree, thus two died after they had received 10 cg, one two hours and the other twenty-four hours after the injection and without any other apparent cause for death than increasing respiratory difficulties. The animals which died after two hours had extensive fat necrosis as demonstrated by Benda's reaction as well as being evident macroscopically. In another animal, which had received 17.5 cg of pilocarpin and which died after eighty-four hours there was found fat necrosis also. It is known that irritation of the vagus causes increased pancreatic secretion but the reason that these two animals developed fat necrosis I have not tried to determine. The rabbit which received the greatest amount of pilocarpin, 35 cg, was moribund at the end of twenty-four hours and was killed, one rabbit is not included among the ten because it lived for seventy-two hours, during which time it received 25 cg four times, dying without any other cause than pilocarpin intoxication. If we exclude the two rabbits which died with fat necrosis we see that altogether three of twenty-five animals were killed directly by pilocarpin.

As there are persons with vagotony, it is reasonable to assume that there may be vagotonic animals also and, as we shall see there are certain signs

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6 Heyrovsky, Hans. *Histologische Untersuchungen der Magenschleimhaut bei Ulcus ventriculi und Carcinom*. *Deutsch. Ztschr. f. Chir.* 122: 359, 1913.

which indicate that the animals which died were previously vagotonic. Eosinophilia is a well known sign of vagotony. Rabbits, however, have not only from 1 to 3 per cent eosinophilic leukocytes normally, but most of the leukocytes in these animals are "pseudoeosinophils." In twenty-five rabbits I found 30 per cent of the leukocytes to be acidophil, and that after injection of pilocarpin the number of acidophil cells increases rapidly in the course of a couple of hours, whereupon the number returns to normal. In fourteen animals, examination of the blood by Jenner's method after injection of pilocarpin, 200 leukocytes being counted each time, showed that ten of the animals on an average had 22 per cent acidophils and 78 per cent other leukocytes before the injection, and after the injection the percentages were 67 acidophils and 33 nonacidophils. Four animals were found to have a larger percentage than usual of acidophils before injection, and it is of great interest to note that these four animals all died, three of them as the direct result of pilocarpin



Fig 1—Hemorrhage into the mucosa in the bottom of a fold, the epithelium absent,  $\times 20$



Fig 2—Definite loss of substance in five hours,  $\times 20$

intoxication and the fourth from fat necrosis. Two of the animals which died from pilocarpin directly received only 10 cg, these animals had 60 per cent eosinophils before the injection, and there was hardly any increase in these cells afterward. It appears, then, when we consider the blood picture before and after injection of pilocarpin in the other rabbits in this series, that the acidophilia in the animals which died may be regarded as indicating an existing vagotony.

In order to learn how the erosions in the stomach developed, I examined this organ in twelve rabbits, all of which had received from 10 to 15 cg of pilocarpin and which died or were killed between two hours and eighteen days after the injection. The erosions, which appeared as dark brown points or stripes, with more or less definite loss of substance, were found in all parts of the stomach, the number varying greatly even with the same dose of pilocarpin. The mucosa was covered with a good deal of mucus in the animals examined about twelve hours after the injection. The first change seemed to

be a hemorrhage into the mucosa (Fig 1), either superficial or extending down to the muscularis mucosae, but always largest at the surface, these hemorrhages were most often round and then rarely more than about 2 mm in diameter, at other times the hemorrhage was more linear, reaching a length of 1 cm at the most. Corresponding to the extravasation there would form, little by little, losses of substance, which would be apparent as early as in two hours. The extravasated blood underwent the usual changes, with the formation of a brownish pigment. The lower part of the mucosa, which was not affected by the extravasation, had normal glands at the end of two hours. At the end of five hours the



Fig 3—Loss of substance extending almost to the muscularis mucosae,  $\times 20$



Fig 4—All blood pigment removed,  $\times 20$

defect was larger, and round cell infiltration and edema made their appearance around it (Fig 2). The defect now enlarged according to the extent of the primary hemorrhage. In the same stomach there would be found after twenty-four hours both wholly superficial defects, nearly free from pigment, as well as narrow slits about to close, and larger losses of substance reaching almost down to the muscularis mucosae, the bottom of which still was covered with pigment. About the defects would be exudate and fairly dense infiltration with cells down into the submucosa. In the bottom of the ulcer would be thrombotic vessels (Fig 3). After forty-eight hours, the largest and deepest

erosion was observed, reaching almost down to the muscularis mucosae, all pigment being removed, the floor being formed by the deepest layer of the mucosa, the structure of which was no longer recognizable, inflammatory exudate and marked leukocytic infiltration extending through the submucosa, in which were thrombotic vessels. The mucosa, which was edematous and



Fig 5—The mucosa seems to have spread out from both sides over the floor which lies on the muscularis mucosae,  $\times 45$

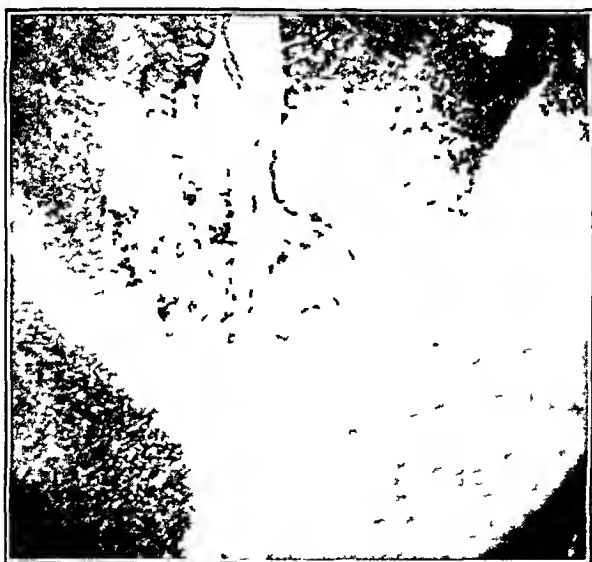


Fig 6—Showing newly formed glandular tubules at the bottom,  $\times 45$

infiltrated with blood about the erosion, had folded itself definitely over the margins (Fig 4) and the process appeared to have become arrested.

After seventy-two hours, the erosions clearly were about to heal. They appeared smaller, the hemorrhagic crust was nearly all removed. In the larger erosions the mucosa had spread itself over the bottom, in which were brownish

pigment and leukocytes (Fig 5) The smaller erosions were covered over, and their site indicated by remnants of blood and pigment along the borders

In two rabbits which were killed after six hours, erosions or scars could not be made out definitely, either macroscopically or microscopically, a third rabbit, however, presented a picture similar to that found after seventy-two hours Of three rabbits which lived ten days, one showed no erosion, another had a small scar-like shrunken area in the larger curvature, shown microscopically to be a depression in the mucosa covered by epithelium without crypts, probably a scar after a deep erosion (Fig 6), the third rabbit showed several erosions, all healing, the process apparently not having gone any further than in animals which had lived three to four days (Fig 7), in one animal which lived eighteen days there were no erosions or scars

The extravasation of blood into the mucosa, which forms the beginning of the erosion, is produced by an irritation of the vagus, but this does not explain how the hemorrhage takes place That the cause is of



Fig 7—Mucosa about to cover the defect,  $\times 45$

a vasomotor nature is not very likely the case, because the vessels of the stomach, so far as known, are innervated only by the sympathetic It seems more likely that it concerns hemorrhages due to circulatory disturbances produced by contraction of the musculature of the stomach, especially the muscularis mucosae, through which the small vessels to the mucous membrane pass The motor nerve of the stomach is the vagus as we know

The loss of substance in the mucosa results from digestion of the tissue damaged by the hemorrhage, and the extent and depth of the loss depends on the extent of the hemorrhage The quantity of pilocarpin injected seems to have no influence on the extent of the extravasation It has been claimed that the injection of pilocarpin increases the secretion of the stomach, particularly the amount of free hydrochloric acid In order to determine whether such



factors play any rôle in the development of the erosions, I aspirated gastric juice before and from two to three hours after the injection. The rabbits studied in this way were living on usual food, such as hay, cabbage and oats. The gastric juice was aspirated through a thin catheter, and usually from 2 to 6 cc was obtained each time. In twenty normal rabbits I found the relation between free hydrochloric acid and total acidity to be on the average 64 105. In eight rabbits the relation before injection of pilocarpin was 75 110, and from two to three hours after the injection it was 43 62. Later the relation was found to be variable. While the erosions develop as early as two hours after the injection of pilocarpin, the hydrochloric acid, as well as the total acidity, diminishes considerably during the first two or three hours after the injection. The stomach contents after the injection were rich in mucus, as stated, the mucosa was found covered with mucus at this time, it is, therefore, probable that it is the increased secretion of mucus which reduces the acidity. In any event, erosions undoubtedly develop even when the acid is reduced. Two animals were given sodium bicarbonate before and one and a half and four hours after the injection, the gastric contents then did not con-



Fig 8—Hemorrhage into the mucosa without destruction of the surface epithelium,  $\times 45$

tain any hydrochloric acid, which was also the case when the animals were killed six hours after the injection. The usual hemorrhages were present in the mucosa but it was not possible to make out any loss of substance, and microscopically, the epithelium over the hemorrhagic area was well preserved everywhere (Fig 8). Hence, it may be concluded that without hydrochloric acid there would be no erosions, that is to say, no loss of substance.

The erosions we have been studying are undoubtedly of the same kind as those which occur after extirpation of the suprarenals. The anatomic picture is precisely the same. Finzi and Mann believe that these erosions are the beginning of possible gastric ulcers. Finzi cites five cases of gastric and duodenal ulcer in which he found changes in the suprarenal after death. Friedman believes that some of the lesions which he observed would have healed in time, but that real ulcers might have developed on the basis of the lesions. My own observations, particularly as regards the appearance of the lesions, the fact that they never go deeper than the muscularis mucosae, and, finally, their marked tendency to heal, lead me to believe that they correspond to the hemorrhagic erosions seen in man. As these erosions in man cannot be regarded as a regular preliminary stage for the development of typical ulcer,

it would be unwarranted to conclude from the experimental and clinical observations at hand that ulcer of the stomach or duodenum results as a consequence of vagotomy or vagus irritation

#### HEMORRHAGIC EROSIONS

Hemorrhagic erosions occur in the human stomach and also in the duodenum. They are superficial, and, as the name indicates, they usually have a hemorrhagic floor. While it is true that there may be only a difference in degree between the simple erosion, especially if the hemorrhagic covering has been removed, and acute ulcer, there rarely are any difficulties in deciding after death whether erosion or ulcer is present. I do not deny that Mann and Friedman may have seen real ulcer develop on the basis of erosions, nor do I claim that an ulcer cannot develop from an erosion. All works on pathologic



Fig 9—Erosion in the human stomach. Hemorrhage in the mucosa and beginning loss of substance,  $\times 45$

anatomy treat hemorrhagic erosions as a peculiar process, which often is distinguished from postmortem changes only with difficulty, the ideas as to their mode of origin and their relation to ulcer are divided.

If the microscopic picture of a hemorrhagic erosion in the human stomach is compared with that of the lesions which develop in the stomach of the rabbit after injection of pilocarpin, there can be no doubt but that it concerns the same process (compare Fig 2 and Fig 9). The question consequently arises whether hemorrhagic erosions in man also depend on vagus irritation.

Beneke<sup>7</sup> has discussed this question in connection with observations of a large number of erosions studied after death in which he no doubt has included certain other conditions than hemorrhagic erosion.

<sup>7</sup> Beneke R. Ueber die hämorrhagischen Erosionen des Magens (stigmata ventriculi), Verhandl d deutsch path Gesellsch 12 284, 1908

strictly speaking He regards the thrombosis in the neighborhood of the erosions as being secondary, and advances the idea that the erosions depend on a transitory ischemia in the mucous membrane produced by reflex irritation of certain nerves, because he found that in a high percentage of the cases there was disease of the central nervous system, and also because he found erosions in persons in whom the celiac ganglion might be injured by operation or peritonitis While one would be inclined to agree with Beneke in regarding the thrombosis as secondary, his theory of a local, brief anemia is not convincing To my mind, the primary lesion is a hemorrhage into the mucosa which reduces the vitality of the tissue Whether this hemorrhage can be referred to a primary irritation of the vagus in the case of man as well as in the case of rabbits is a question on which I shall try to throw light by means of certain cases I have gathered the cases of definite, unquestionable hemorrhagic erosions which I have observed in the course of the last two years in this institute As definite hemorrhagic erosions I regard larger or smaller superficial defects in the mucosa with a dark brown floor, which have developed during life, as shown by thrombosis, pigmentation and more or less round cell infiltration Hemorrhagic erosions of this sort have been observed in ten cases postmortem, five times in the stomach and in the duodenum Fifteen erosions were examined microscopically, thrombi were not always present, bacteria were not demonstrable, and the mucous membrane around the erosions was always normal without signs of gastritis

#### SUMMARY OF CASES

CASE 1—Man, aged 52, otitis media and diffuse meningitis, pulse, 120, died on day of admission to hospital

CASE 2—Woman, aged 21, otitis media, operation, death five days later with large abscess in cerebellum Pulse, at entrance, 88, day before death, 60, shortly before death, 120

CASE 3—Man, aged 32, tuberculous meningitis, pulse 52, death

CASE 4—Man, aged 37, diffuse meningitis after otitis media, pulse, 88, death

CASE 5—Man, aged 25, miliary tuberculosis, marked meningeal symptoms, pulse from 88 to 100, death in four days

CASE 6—Woman, aged 20, tuberculous meningitis, pulse increased gradually during ten days from 104 to 140

CASE 7—Man, aged 25, in hospital two and a half months with tuberculosis of the lung and of the hilum glands, the pulse, at first very slow, became suddenly rapid, choked disks

CASE 8—Man, aged 56, had sarcoma in lymph glands with metastases in the pleura, died from asphyxia, pulse at first 100, at time of death, fourteen days later, 144

CASE 9—Man, aged 24, pulmonary disease following influenza, the upper and middle lobes infiltrated, thrombi in right ventricle

CASE 10—Man, aged 60, intestinal obstruction, pulse, 60, diffuse peritonitis, operation, death soon after, pleural empyema

## COMMENT

There can hardly be any question that in the first group of six cases of this series irritation of the vagus was produced during the course of the illness which in every case was situated in the brain or its membranes. In the second group of three cases the disease involves the chest, the lungs and pleura being the seat of infiltrating processes. In Case 7 the very slow pulse, subsequently becoming rapid, indicates affection of the vagus. In a case of cancer of the breast with metastases in the lung and pleura described by Lyder Nicolaysen,<sup>8</sup> there was infiltration of the vagus and symptoms of vagus paralysis. In Case 10, one of peritonitis with empyema, it is possible that there may have been involvement of the nerves of the stomach in the abdomen as well as in the thorax, although the proof that such was the case cannot be supplied.

The vagus nerves and the nerves of the stomach in these ten cases should have been examined microscopically, but the material was gathered originally in the course of a study of ulcer of the stomach, it was only later that my attention was directed to the hemorrhagic erosions of the stomach in these cases. The result of the study shows that in most of the cases in which hemorrhagic erosions were found, there had been irritation of the vagus or the possibility of such irritation. To conclude from these cases that hemorrhagic erosions always result from irritation of the vagus does not seem warranted. It is possible that in some of these cases it concerns a coincidence. However, Benke's results and the pilocarpin experiments in rabbits favor the conclusion that vagus irritation may cause erosions. Further studies of suitable material should be made and with careful microscopic examination of the vagus.

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<sup>8</sup> Nicolaysen, Lyder. Et Tilfælde af Vaguslammelse, Norsk Mag f Lægevidensk 77 948, 1916

# CLINICAL STUDIES ON THE RESPIRATION

## VI A COMPARISON OF VARIOUS STANDARDS FOR THE NORMAL VITAL CAPACITY OF THE LUNGS\*

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As the clinical value of determinations of the vital capacity of the lungs becomes more clearly emphasized—in heart disease, in tuberculosis, in aeronautics, etc—the problem of normal standards becomes increasingly important. For the clinician, the standard should require as few and simple measurements as are consistent with reasonable accuracy.

Since the earlier studies on this subject, it has been recognized that healthy individuals vary considerably in the volume of air which they can expire after a full inspiration. Age, sex, height, weight, the size and flexibility of the chest, muscular strength and physical training are factors which may singly or jointly affect the vital capacity. As an example, trained soldiers, and especially athletes, tend to show higher vital capacity readings than clerks of the same age, height and weight. The probability, therefore, of finding a single standard for all classes of individuals that does not involve numerous measurements and complicated formulas, and that is at the same time not subject to rather wide variations is, to say the least, remote.

Since Hutchinson's<sup>1</sup> admirable studies in 1846, various methods of approach to the problem have been tried. Hutchinson was the inventor of the spirometer, and his observations were unusually extensive and carefully made. After studying various measurements of the body in nearly two thousand healthy individuals from various classes and occupations, he concluded that the vital capacity varied more closely with differences in height than with any other known variable. Consequently, he adopted the following rule: "For every inch in height (from five feet to six feet), eight additional cubic inches of air at 60 F are given out by a forced expiration."

Since this time the majority of workers have followed Hutchinson's method of using the height as the factor in determining the vital capacity normal for each individual. The method has been subject to much criticism on the basis that the individual variations for each height are too great, and numerous attempts have been made to substitute other measurements and formulas. Most of these have, however, been equally unsatisfactory, and have not been widely used.

Three of the more recent contributions must be considered in some detail. Peabody,<sup>2</sup> in his studies of the respiration, has demonstrated

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1 Hutchinson, Jonathan. *Med Chir Tr*, London 29 137, 1846.

2 Peabody, F W. *The Harvey Lectures*, 1916-1917, also, *Am J M Sc* 155 100, 1918.

the importance of reduction in the vital capacity as an index of the tendency to dyspnea in cardiac disease, and has emphasized the importance of vital capacity determinations in diagnosis, prognosis and treatment. He, with Wentworth, studying the vital capacities in a series of 140 healthy persons, largely medical students and nurses, found that, according to their height, they fell into three groups for each sex, and the average vital capacity for each group was taken as the normal standard. From ninety-six normal males, "Group I includes those who were 182.5 cm (6 feet) tall or over, and the normal standard computed was 5,100 c c. Group II consisted of men between 173.5 cm (5 feet, 8½ inches) and 182.5 cm (6 feet) tall, and the average vital capacity, which was 4,800 c c, was taken for the normal. Group III was comprised of persons whose height was between 173.5 cm (5 feet, 8½ inches) and 159.5 cm (5 feet, 3 inches). The normal standard for this group was 4,000 c c." Of these ninety-six men, 84 per cent were within 10 per cent of normal. "The women were also subdivided into three groups according to their height. Group I was composed of those who measured over 167 cm (5 feet, 6 inches) tall, and the average vital capacity was 3,275 c c. Group II consisted of those who were from 162 cm (5 feet, 4 inches) up to and including 167 cm (5 feet, 6 inches). The normal standard for this group was found to be 3,050 c c. Group III was made up of persons from 154.5 cm (5 feet, 1 inch) up to and including those who were 162 cm (5 feet, 4 inches) tall. The standard vital capacity for this group was 2,825 c c."

Peabody and Wentworth<sup>3</sup> also studied the relationship of the vital capacity to the body surface area in a small group of individuals, and finding a very close agreement, suggested that further studies on this line might be of considerable value.

Lundsgaard and Van Slyke<sup>4</sup> in a series of eighteen normal men and women found that the vital capacity varied more closely with the calculated chest volume than with the height. They determined the chest volume by making use of the following measurements: "The height of the chest is taken as the length of the sternum from incisio intraclavicularis to a point just below articulatio sternoxiphoidea. The depth is then taken as the horizontal distance from the middle of the sternum at the insertion of the third rib to the spinal column, and the breadth is the distance across the sixth ribs in the midaxillary line." The product of these figures taken with the chest at rest, the "middle chest volume," gives a value which is "approximately proportional" to the real chest volume. Certain precautions in taking these measurements must be observed, for the details of which the original article

<sup>3</sup> Peabody, F. W., and Wentworth, J. A. *Arch. Int. Med.* 20:443 (Oct.) 1917.

<sup>4</sup> Lundsgaard, Christen, and Van Slyke, Donald R. *J. Exper. M.* 27:65, 1918.

should be consulted. The average ratio, as found by Lundsgaard and Van Slyke, between the vital capacity and the middle chest volume was 45  $\frac{(100 \times \text{chest volume})}{\text{vital capacity}} = 45$ ). The observations by which

this value was determined included both the males and the females.

Since the determinations of the present report were made, Dreyer<sup>5</sup> has published an excellent study of normal vital capacity standards. He shows that certain relations may be expressed, and arranges them in the order of their importance as follows:

"1 The vital capacity is a function of the *weight*. This can be expressed in the formula  $\frac{W^n}{V C} = K$ , where  $W$  is the net weight of the body expressed in grams,  $V C$ , the vital capacity expressed in cubic centimeters, and the power  $n$  is approximately  $\frac{2}{3}$ , though more accurately 0.72, and  $K$  is a constant. As it is already established that  $\frac{W^n}{S} = K_2$  where  $W$  = net weight,  $S$  = body surface, and the power  $n$  is approximately  $\frac{2}{3}$  though more accurately 0.72, it follows that *the vital capacity is a simple function of the body surface*. In other words, that the smaller and lighter individual, with his relatively larger surface, has a greater vital capacity per unit of body weight than the larger individual.

2 The relation between the vital capacity and *stem length* can be correctly expressed by the formula  $\frac{V C}{\lambda^n} = K_3$  where  $\lambda$  = stem length in centimeters,  $V C$  = vital capacity in cubic centimeters, the power  $n$  is approximately 2, and  $K_3$  is a constant.

3 The relation between vital capacity and *circumference of chest* can be expressed by the formula  $\frac{Ch^n}{V C} = K_4$  where  $Ch$  = circumference of chest expressed in centimeters,  $V C$  = vital capacity expressed in cubic centimeters, the power  $n$  is approximately 2, and  $K_4$  is a constant.

4 Finally,  $\frac{\lambda \times Ch}{V C} = K_5$  where  $\lambda$  = stem length in centimeters,  $Ch$  = circumference of chest in centimeters,  $V C$  = the vital capacity in cubic centimeters, and  $K_5$  is a constant."

In applying these formulas, Dreyer found that the limit of error in the relation between the body surface and the vital capacity was comparatively slight, but becomes progressively greater in the succeeding formulas. He discards standards based on the height alone as being subject to too wide individual variations.

The formula  $\frac{W^{2/3}}{S} = K$  is that of Meeh modified to  $\frac{W^{0.72}}{S} = K$  in earlier studies of Dreyer with Ray and Walker<sup>6</sup> as being more nearly correct for determining the area of body surface.

5 Dreyer, Georges. *Lancet* 2 227 (Aug. 9) 1919.

6 Dreyer, Ray and Walker. *Proc. Roy. Soc. Med., Series B* 86 39, 56, 1912.

It is suggested that the other formulas, though showing greater inaccuracies, may be of considerable value in determinations in pathologic cases where the weight has become abnormal

The average value of the constant  $K$  in the formula,  $\frac{W^n}{V C} = K$ , determined in Dreyer's series of sixteen carefully studied persons was found to be 0.380 when the power  $n$  is taken as  $\frac{2}{3}$  and 0.690 if 0.72 is taken as the value of  $n$

Professor Dreyer carefully points out, however, that there is a variation in the value of  $K$  if groups of individuals are studied whose nature of life and habits are distinctly different. This variation has previously been mentioned and suggests that in applying such standards for comparison of vital capacities, values must be determined for the various important classes of individuals and that these must be revised as conditions of life change in order to maintain a high degree of accuracy.

Lundsgaard and Van Slyke and Dreyer have shown the importance of vital capacity measurements in studying cases of pulmonary tuberculosis and their value in diagnosis, in prognosis and in gauging the effect of treatment.

The observations reported in this paper were undertaken for the purpose of applying various standards to the same group of individuals so that the variations in these standards might be compared.

The eighty-five men were nearly all members of the first year class in the Harvard Medical School, and were unselected, except that all were free from pulmonary or cardiac disease. They showed rather wide variation in physical type, from the habitually sedentary student to the college athlete. They, therefore, represent fairly well the average young men of their age seen in every-day life. The women were nearly all nurses from the Peter Bent Brigham Hospital, and were somewhat more carefully selected in that all were required to pass physical examinations before being admitted to the training school. No further selection than this was made.

The following measurements were recorded: Age, height in cm without shoes, weight in kg without clothes, chest volume by the method of Lundsgaard and Van Slyke, and the vital capacity in c c. The latter was determined with the simple calibrated cylindrical spirometer of about eight liters capacity as described by Peabody. Several trials were allowed, a minimum of three, and the largest expiration recorded was taken as the vital capacity. From the height and weight the surface area was computed by the formula of DuBois and DuBois,<sup>7</sup>  $\text{area (sq cm)} = \text{wt}^{0.425} \times \text{ht}^{0.725} \times 71.84$ , the weight being in grams and the height in centimeters. The formula has been

<sup>7</sup> DuBois, Delafield and DuBois, Eugene F. Arch. Int. Med. 15: 868, Pt. 2 (June) 1915.



shown to be more accurate than Meeh's formula  $\frac{W^{\frac{2}{3}}}{S} = K$ . In order to eliminate extensive calculations, DuBois and DuBois have published a graphic chart by which the surface area can readily be determined if the height and weight are known. This method was used.

The data on the men and women were kept separate, and are tabulated in Tables 1 and 2. Values for the direct ratio between the vital capacity and height were computed and the average for the men was found to be 26.5. Since there is a comparatively large number of men with athletic training in the group who have unusually high vital capacities, the value 25 was arbitrarily chosen as being for practical purposes near to the normal of the average individual. And further, since all known pathologic conditions affecting the vital capacity do so by reducing it (witness heart disease and tuberculosis) it is much better to have standards which err in relation to high normals than to low normals. The data on the normals of Dr. Peabody were made available, and the average for the same ratio in his men was found to be 26.3. For the women the actual average was 20.6. The value 20 was assumed as the standard. Using 25.1 as the ratio for men and 20.1 as the ratio for women, 63 per cent of the combined groups (129 persons) were seen to have vital capacities within 10 per cent of the assumed normal. Only 5 per cent of the group fell below 90 per cent of the normal. The remaining 22 per cent were higher than normal and were chiefly represented by those individuals having athletic training.

Using Peabody's group standards, 54 per cent of the combined groups had vital capacities within 10 per cent of the normal and 10 per cent of the remainder were below 90 per cent. It is interesting that Peabody found such a close agreement in his series, using these standards. However, there are obvious objections to this method which those who have used the standard have undoubtedly discovered. The chief of these is the wide differences found in individuals whose height places them at the extremes of the various groups. For instance, a man 174 cm. tall, by this method should have a vital capacity of 4,800 c.c., while a man 173 cm. tall would be expected to have a vital capacity of only 4,000 c.c. In addition, the method is complicated and the various values are hard to remember.

The average value for the chest volume ratio was approximately 63 for the men and 56 for the women. With these values as standards, 69 per cent of the combined groups were found to have vital capacities between 90 and 110 per cent, while 21.5 per cent were below 90 per cent. On the other hand, when the value for the ratio adopted by Lundsgaard and Van Slyke (45) was used as the standard, only 8 per cent of the 129 persons had vital capacities within 10 per cent of the normal and 81 per cent were over 120 per cent of the normal.

Finally, we find that the most consistent relationship exists between the vital capacity and the area of the body surface. The actual average for the men was 261 L per sq m of body surface, and for the women 207 L per sq m, 25 L per sq m and 20 L per sq m were chosen as more convenient standards and as in the height ratio giving slightly less influence to the presence of the unusually high vital capacity found in some of the individuals observed. By these standards 71 per cent were found to have vital capacities within 10 per cent of the normal and only 5.5 per cent were below 90 per cent. It was interesting and gratifying to discover that when the formula of Dreyer,  $\frac{W^{0.72}}{V \cdot C} = K$  was used later, and the values for  $K$  were taken as the averages found in these two groups (in eighty-five men  $K = 0.632$ , in forty-four women  $K = 0.807$ ), almost identical results were obtained, the number having vital capacities within 10 per cent of the normal by this method being only about 2 per cent less than when the formula of DuBois and DuBois was used.

In the accompanying chart curves have been constructed showing these results in graphic form. The ordinates represent the number of observations as expressed in per cent of the combined groups, men and women, the abscissae represent the relation in per cent to the various standards, the normal given as 100 per cent.

In Table 1 the asterisk before the initials indicates those men who have done more than the usual amount of athletic work. This consisted chiefly in high school and college foot ball, basket ball, track, base ball, swimming, rowing, etc. It is to be noted that all of the men having vital capacities of more than 5,300 c c are of this group. Six men having vital capacities of more than 5,000 c c but not more than 5,300 c c gave no history of unusual athletic training. For this trained group the average values for the various ratios may be seen in Table 3. They are noticeably higher than the averages for the whole group.

No particular reason was found for the few vital capacities that were considerably lower than the general average.

From these data, as well as from the work of Dreyer, it would appear that the most accurate method for calculating the normal vital capacity for an individual is from a standard based on the surface area. In using a value for this standard, whether as expressed in c c per square meter of body surface or an arithmetical value as a constant as in the formula  $\frac{W^{0.72}}{V \cdot C} = K$ , it would seem that allowance must be made for the past physical training and experience of the individual. Professor Dreyer's tabulation of the observations of Hutchinson on

TABLE 1—ANALYSIS OF FINDINGS IN EIGHTY-FIVE NORMAL MEN

	Age	Vital Capacity, C c (A)	Height, Cm (B)	Weight, Kg (C)	Body Surface Area, Sq M (D)	Chest Volume, l (E)	$\frac{A}{B}$	$\frac{A}{D}$	$\frac{100 A}{E}$ (expressed in C c)	Percentage Relation to Standards			
										$\frac{A}{B} = 25$	$\frac{A}{D} = 2.5$	$\frac{100 A}{E} = 45$	$\frac{100 A}{E} = 63$ (Average of this group and Van Slyke)
F C F*	20	6,700	187.0	80.4	2.06	9.06	35.8	3.25	74.0	143	130	164	117
G O C*	25	6,500	195.5	85.6	2.18	8.12	33.3	2.93	80.0	133	119	178	127
D B*	21	6,200	180.5	79.0	1.99	9.18	34.4	3.11	67.5	138	124	150	107
F B D*	23	5,800	179.5	71.6	1.90	7.80	32.3	3.05	74.4	129	122	165	119
H B G*	20	5,700	185.0	77.0	2.03	8.38	30.6	2.84	68.8	122	114	153	109
J S*	24	5,700	174.5	72.4	1.87	10.30	32.7	3.05	55.4	131	122	123	88
F M S*	23	5,700	186.0	70.2	1.93	10.92	30.7	2.95	52.2	123	118	116	83
G E D*	23	5,500	179.0	64.6	1.82	6.52	29.0	3.02	84.2	116	121	187	134
A C R*	28	5,450	177.7	70.6	1.88	9.24	30.7	2.90	79.0	123	116	131	94
A V D*	36	5,300	181.0	80.8	2.01	9.49	29.2	2.64	59.9	117	106	124	95
H L R*	22	5,300	163.0	63.3	1.72	7.66	31.5	3.08	69.2	126	123	154	110
E F M*	33	5,300	181.5	70.4	1.90	8.82	29.2	2.79	60.1	117	112	134	96
R C McL	22	5,300	181.8	74.4	1.95	6.54	29.2	2.72	81.0	117	109	162	129
M R.	21	5,200	180.0	67.2	1.86	8.12	28.9	2.80	64.1	116	112	143	102
O H E*	30	5,200	175.5	61.5	1.76	6.87	29.6	2.95	75.7	118	113	168	120
W W H*	23	5,200	173.5	65.0	1.78	7.05	30.0	2.92	73.4	120	117	163	112
K L M*	21	5,200	174.5	64.4	1.78	7.70	29.8	2.92	67.5	119	117	150	107
R L L	21	5,150	170.5	64.4	1.75	8.69	30.2	2.94	63.7	121	118	142	101
A Q	23	5,100	174.0	61.6	1.75	8.82	29.3	2.91	57.8	117	116	129	92
T P K*	22	5,000	179.5	65.2	1.83	7.32	29.9	2.73	68.4	112	109	152	109
E A E	30	5,000	175.0	78.5	1.94	9.64	28.6	2.53	51.9	114	103	115	82
R A D	25	5,000	173.0	64.3	1.78	8.03	28.9	2.81	62.3	116	112	138	99
J W M*	24	5,000	183.0	75.2	1.97	7.70	27.3	2.54	65.0	109	102	144	103
W H V W*	23	5,000	170.8	64.1	1.75	6.81	29.3	2.86	73.4	117	114	163	116
S H	24	4,900	166.8	65.0	1.73	7.84	29.7	2.87	63.3	119	115	141	100
D O G	22	4,900	169.0	66.0	1.77	6.80	29.0	2.77	72.1	116	111	160	100
J P*	36	4,900	169.0	72.0	1.83	9.45	29.0	2.68	51.8	116	107	115	114
H J S*	24	4,900	182.5	68.2	1.81	6.94	28.4	2.71	70.6	108	108	157	112
S G	24	4,850	179.0	63.6	1.80	7.05	27.1	2.69	68.6	104	103	152	109
J R W*	21	4,850	175.8	67.8	1.83	8.25	27.6	2.65	58.8	110	106	131	93
H B	24	4,850	175.0	60.5	1.74	8.10	27.7	2.79	59.9	111	112	133	95
G W T*	22	4,800	171.0	65.0	1.77	8.02	28.1	2.71	59.9	112	108	133	95
T L P	21	4,800	178.0	65.2	1.82	6.70	27.0	2.64	71.7	108	106	159	114
H D*	22	4,750	176.0	66.0	1.81	7.13	27.0	2.62	66.6	108	105	148	106
S N G	23	4,700	176.0	60.2	1.74	7.03	26.7	2.70	66.9	107	108	149	106
L V H	22	4,700	177.0	74.2	1.91	7.72	26.6	2.46	60.9	106	93	135	97

F P K	21	4,700	178 0	62 4	1 78	7 22	26 1	2 64	65 1	98	106	106	108	145	103
G K	21	4,700	171 0	63 5	1 75	7 18	27 5	2 69	65 5	118	110	110	108	147	104
M J M *	21	4,700	182 0	70 5	1 91	7 40	28 8	2 46	68 6	98	103	98	98	141	101
L W	21	4,700	169 0	74 4	1 85	6 85	27 8	2 51	68 6	118	111	111	102	153	109
E J R	22	4,600	170 4	68 0	1 74	8 10	27 3	2 69	57 5	116	109	108	108	138	91
L W	21	4,600	174 0	68 0	1 82	7 71	26 4	2 53	50 7	96	106	106	101	133	95
H P S	21	4,600	173 5	65 2	1 79	6 25	26 5	2 57	73 6	96	106	103	103	164	117
F V G *	22	4,600	173 5	68 0	1 84	7 79	26 5	2 57	59 0	96	106	100	100	131	94
J L G	22	4,520	174 0	57 0	1 69	7 00	26 0	2 67	61 6	92	106	104	107	144	102
G G S	10	4,500	167 3	62 5	1 70	6 73	26 9	2 65	66 8	113	108	106	106	149	106
H B S	23	4,500	187 5	57 5	1 79	6 40	24 0	2 51	70 4	88	106	100	100	158	112
J R G	25	1,500	170 0	53 5	1 62	6 03	26 5	2 78	74 6	113	106	111	111	166	118
R W B *	21	1,500	164 3	62 2	1 68	7 89	27 4	2 68	57 1	113	110	107	107	127	91
J W M *	26	4,450	173 8	57 6	1 69	6 34	25 6	2 63	70 2	93	102	105	105	156	111
M	22	4,400	161 5	59 5	1 63	7 40	27 3	2 70	59 5	110	109	108	108	132	95
W A K	19	4,400	173 5	64 8	1 78	7 64	25 4	2 17	57 6	92	102	99	99	138	92
F M F *	21	4,400	177 8	71 6	1 89	8 16	24 1	2 33	54 0	92	99	93	93	123	86
H T O	18	4,400	183 0	70 8	1 92	9 81	26 1	2 39	44 9	86	97	92	92	100	71
W P	22	4,350	163 3	60 0	1 65	7 49	26 6	2 64	58 0	109	106	106	106	129	92
B N S	21	4,300	169 0	67 4	1 78	6 86	25 5	2 42	62 7	108	102	97	97	140	100
R L M	23	4,300	174 0	57 2	1 69	7 00	24 7	2 54	61 4	90	99	102	102	136	98
Mek	21	4,300	179 0	60 2	1 77	7 08	24 0	2 43	60 8	90	96	97	97	135	97
W W F	26	4,300	167 5	53 8	1 67	8 26	25 7	2 57	52 0	108	103	103	103	116	83
D H F	19	4,300	166 0	64 8	1 72	7 70	25 9	2 50	55 8	108	104	100	100	124	89
J P O S	21	4,250	172 5	62 2	1 74	6 24	24 6	2 44	68 1	106	93	98	98	151	108
E O S	23	4,210	180 2	55 5	1 71	6 80	23 3	2 46	61 0	88	93	88	83	138	98
J T S	21	4,200	175 6	65 8	1 81	8 10	23 9	2 32	52 0	96	96	93	93	116	83
O W S	22	4,200	167 5	51 4	1 57	5 16	25 1	2 68	81 4	105	100	107	107	181	129
J P P *	26	4,200	172 0	57 3	1 68	6 47	24 4	2 50	64 8	105	98	100	100	144	103
O F O B *	23	4,200	165 0	56 3	1 62	5 38	25 5	2 59	78 1	105	102	104	104	174	124
B I G	22	4,200	171 0	57 4	1 67	7 36	24 6	2 52	57 1	105	98	101	101	127	91
A J P	23	4,100	171 5	57 0	1 67	8 92	23 9	2 45	46 0	103	96	98	98	162	73
T J O	22	4,100	174 0	64 0	1 78	7 25	23 6	2 40	56 6	85	94	94	94	126	90
S I S	22	4,050	166 3	59 8	1 67	7 62	24 4	2 43	53 1	101	93	97	97	118	84
P J K	21	4,050	172 0	57 3	1 68	6 56	23 5	2 41	61 7	101	94	96	96	137	98
H T H	23	4,050	172 2	60 9	1 72	7 00	23 5	2 35	57 9	101	94	94	94	129	92
H I B	21	4,050	172 5	55 9	1 67	7 01	23 5	2 43	57 8	101	94	97	97	128	92
H M	20	4,000	169 5	60 0	1 69	6 60	23 6	2 37	60 6	100	94	95	95	135	96
M L	21	4,000	173 6	58 7	1 70	7 38	23 0	2 35	54 2	83	92	94	94	120	86
L S	21	3,950	169 0	58 8	1 68	5 76	23 4	2 35	68 6	92	94	94	94	152	109
O A B	26	3,910	174 5	72 0	1 87	7 21	22 4	2 09	54 2	89	90	84	84	121	86
M K	21	3,900	160 6	53 4	1 55	5 65	24 3	2 82	69 0	98	97	101	101	153	109
B E B	21	3,900	167 0	62 5	1 70	6 78	23 4	2 29	57 5	98	94	92	92	128	91
W F H	22	3,750	175 5	53 8	1 72	5 82	21 4	2 18	64 4	78	86	87	87	143	102
J G	21	3,750	168 5	56 5	1 64	6 80	22 3	2 29	55 2	94	89	92	92	123	88
R L M	22	3,650	160 7	57 3	1 60	5 72	22 7	2 28	63 0	91	91	91	91	142	101
M F O	27	3,600	157 5	62 0	1 63	6 28	22 9	2 21	57 4	90	92	88	88	128	91
W J M	22	3,500	162 8	56 0	1 60	6 53	21 5	2 19	53 6	88	86	88	88	119	85
E A McV	23	3,400	166 9	58 0	1 65	6 70	20 4	2 06	50 1	85	82	82	82	111	80

\* Men who have done more than the usual amount of athletic work

TABLE 2—ANALYSIS OF FINDINGS IN FORTY-FOUR NORMAL WOMEN

	Age	Vital Capacity, Cc (A)	Height, Cm (B)	Weight, Kg (C)	Body Surface Area, Sq M (D)	Chest Volume, l (E)	A — B	A — D	100 A — E (expressed in Cc)	Percentage Relation to Standards			
										A — B	A — D	$\frac{100 A}{E} = 45$ (Lunds gaard and Van Slyke)	$\frac{100 A}{E} = 56$ (Average of this group)
I G	22	4,150	170.5	85.8	1.98	8.60	24.3	2.10	48.3	127	122	107	86
J D	19	4,000	163.9	61.2	1.67	6.57	23.4	2.40	61.0	131	122	135	109
A F	23	3,950	169.0	72.3	1.83	6.72	23.4	2.16	58.8	121	117	131	105
M P	22	3,900	160.4	51.6	1.53	6.06	24.3	2.55	64.0	138	122	143	114
L V	23	3,900	167.7	58.4	1.68	6.53	23.3	2.82	59.7	119	117	133	106
N T	22	3,900	171.6	54.6	1.64	5.94	22.7	2.38	65.7	119	114	146	117
M G	26	3,900	166.3	66.2	1.74	7.96	23.5	2.24	49.0	128	118	109	88
M I	28	3,800	164.9	69.6	1.77	7.90	23.0	2.15	48.2	125	115	107	86
F J	21	3,700	167.3	61.0	1.69	5.52	22.1	2.19	67.0	113	111	149	120
L T	20	3,700	166.6	60.8	1.68	6.20	22.2	2.20	59.7	121	111	133	107
H L	27	3,600	167.2	66.4	1.75	6.40	21.5	2.06	56.3	110	108	125	100
E G	24	3,600	163.5	61.2	1.67	6.00	22.0	2.15	54.6	118	110	121	98
M R S	24	3,600	164.1	61.2	1.67	5.88	21.9	2.15	61.2	118	110	136	109
B B	36	3,550	167.2	62.0	1.70	6.84	21.2	2.09	52.0	108	106	108	93
G P	27	3,550	163.4	53.4	1.57	6.34	21.7	2.26	66.0	107	103	124	100
A P	21	3,500	170.8	60.4	1.70	5.64	20.5	2.06	56.0	116	109	138	111
H B	56	3,500	156.9	44.6	1.41	5.40	22.3	2.48	64.8	124	112	144	116
E O	25	3,450	168.3	61.8	1.74	6.72	20.8	2.01	52.1	107	104	116	98
M M	19	3,350	166.7	67.2	1.75	6.90	20.7	1.97	50.0	113	104	111	89
J H	19	3,300	159.3	62.0	1.62	7.31	21.4	2.07	45.8	118	107	102	82
M J	25	3,300	159.7	56.4	1.58	5.56	20.7	2.11	59.4	117	104	132	106
O B	21	3,300	166.5	50.0	1.50	5.10	20.7	2.20	64.6	117	104	144	115
L P	21	3,300	160.5	49.2	1.50	5.74	19.8	1.94	57.5	108	99	128	103
K G	25	3,330	154.7	57.4	1.55	5.34	21.5	2.15	61.8	117	103	137	110
P H	23	3,250	164.0	52.6	1.57	5.50	19.8	2.07	60.6	118	108	135	108
M K	27	3,250	166.2	56.0	1.62	5.70	19.8	2.07	57.0	107	99	127	102
L B	23	3,200	162.4	60.4	1.64	5.92	19.7	2.01	59.0	107	98	131	105
H H	20	3,200	163.0	50.7	1.64	5.62	19.6	1.95	65.0	105	99	145	116
V M	39	3,200	163.5	50.7	1.53	5.82	19.6	2.00	57.0	112	98	127	102
A M H	23	3,150	161.5	60.0	1.65	5.80	19.6	2.00	58.0	105	98	129	104
M B	28	3,100	168.6	50.6	1.52	6.15	19.5	1.94	46.7	105	98	104	84
M G	24	3,100	160.7	54.0	1.60	6.40	18.4	2.07	51.4	112	98	114	92
M W	33	3,100	155.8	55.6	1.68	6.73	19.3	1.94	48.5	95	92	108	87
H N	30	3,100	165.5	61.0	1.54	5.74	19.9	1.84	46.1	110	97	108	82
M McD	19	3,000	159.5	52.2	1.68	6.00	18.7	1.84	51.6	110	100	120	97
D H	20	3,000	162.8	62.2	1.52	5.52	18.8	1.97	54.4	106	94	115	92
R O	18	3,000	165.7	61.6	1.67	8.44	18.4	1.80	35.6	99	92	121	97
L H	21	2,900	160.0	51.0	1.68	5.00	18.1	1.80	60.0	99	90	79	64
M D	26	2,800	155.7	58.6	1.52	4.41	18.1	1.91	65.8	103	91	133	107
L M	19	2,800	163.3	57.0	1.59	5.74	18.0	1.70	35.7	99	84	146	87
R F	24	2,600	163.7	42.1	1.42	3.82	15.9	1.71	68.0	85	80	80	64
W O	20	2,500	156.5	42.8	1.39	4.21	16.0	1.80	59.4	89	80	132	106

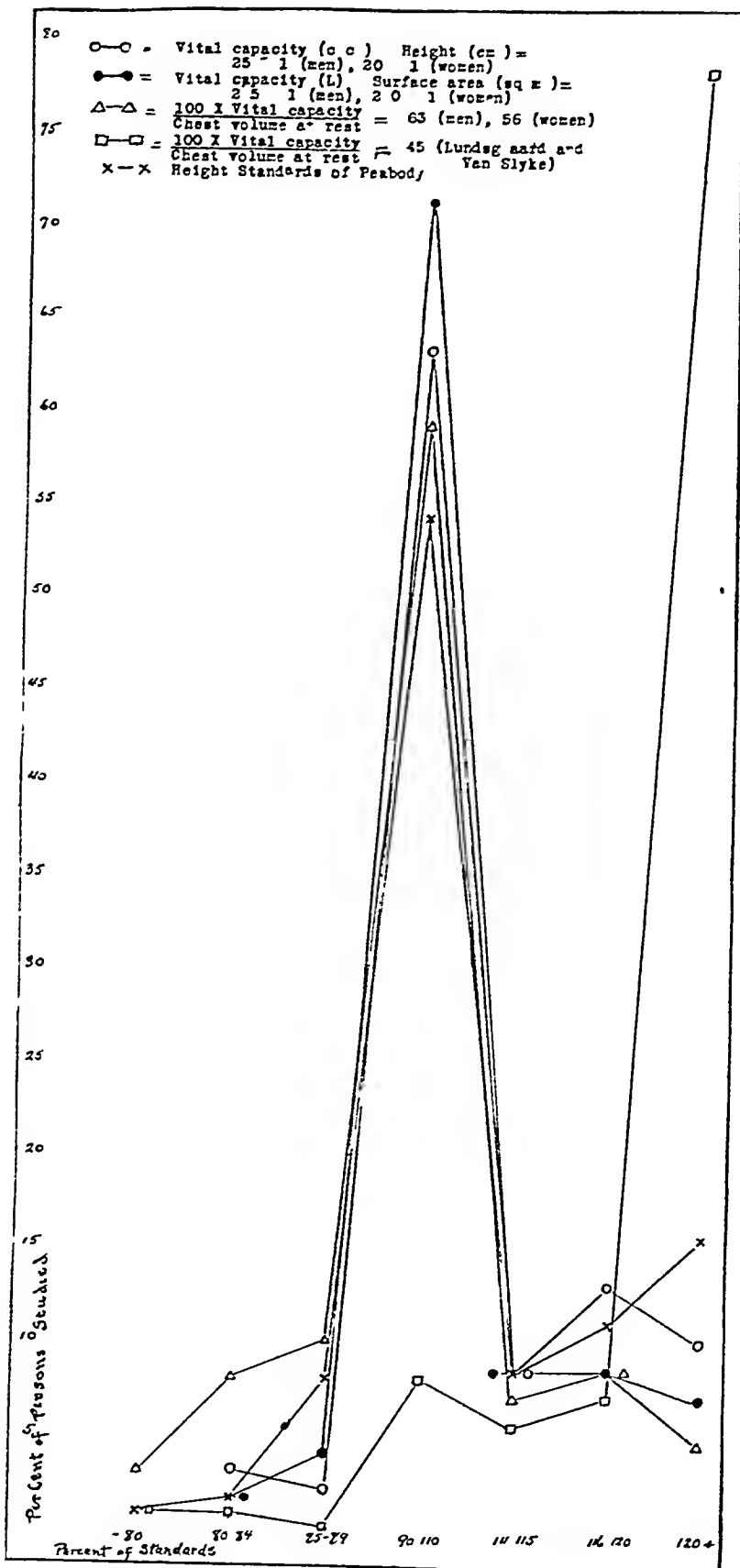


Chart showing percentage of persons in relation to normal standards  
 Ordinates Percentage of group (129 persons) Abscissae Percentage of  
 standards used The group falling on the abscissa 90-110 includes those indi-  
 viduals whose vital capacities fell within 10 per cent of the normal

this basis is the most complete comparison of this type so far available. It is to be hoped that similar extensive observations of the more important groups representative of the habits of life of the present day may soon become available. In addition, it is very desirable that more observations be made on elderly individuals, for age apparently reduces the vital capacity to an appreciable extent.

TABLE 3—SUMMARY OF RATIO VALUES

	Men	Women	Athletes
Vital capacity height	25.0	20.0	29.0
Vital capacity body surface area	2.5	2.0	2.8
100 × vital capacity chest volume	63.0	56.0	67.0
$\frac{W^{0.072}}{V \cdot C}$	0.632	0.807	0.591
$\frac{W^{2/3}}{V \cdot C}$	0.350	0.450	0.326

For quick clinical work, where it is not practicable to obtain the net weight of the patient nor to make extensive measurements, a simple comparison between the vital capacity and the height will give a value which will closely approximate the normal for that individual, though individual variations by that method are greater than when the surface area is used. According to the chart, however, it is seen that practically the same number of low values were found by the two methods. While the greatest proportion of vital capacities studied were within 10 per cent of the normal, too much weight should not be given to single determinations, unless a variation of more than 15 per cent from the chosen standard is obtained.

## SUMMARY

A group of 129 persons are studied for the purpose of comparing various standards for determining the normal vital capacity.

A standard based on the body surface area is advised, since it has been shown that the vital capacity varies with this function more uniformly than with others tried.

When the weight of the patient cannot be obtained, a standard based on the height is recommended.

I desire to express my appreciation to Miss B. I. Barker and Dr. T. D. Cunningham for their valuable assistance in accumulating and compiling the data used in these observations.

# EXPERIMENTAL DETERMINATION OF THE INFLUENCE OF ABNORMAL CARDIAC RHYTHMS ON THE MECHANICAL EFFICIENCY OF THE HEART \*

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## INTRODUCTION

The occurrence of an abnormal cardiac rhythm clinically involves two important and essentially different considerations. First, the information it may give as to the general pathologic condition of the heart and the prognosis of the disease, and second, the mechanical influence it exerts on the pumping action of the heart. The normal heart beat, in which there is a regular succession of auricular systoles within certain rates, each of which is followed after a definite interval by contraction of the two ventricles, is best adapted to the function of the heart as a pump. Anything which seriously interferes with the normal rate or coordination of beats, interferes, to a certain extent, with the mechanical efficiency of the heart. An excessive rate of contraction, even though the regularity and coordination of beats is maintained, reduces the amount of blood pumped by the heart by shortening and rendering insufficient the period during which the ventricles fill with blood from the auricles <sup>1</sup>

It is interesting to note in this connection that owing to the rapid period of ventricular filling immediately following ventricular systole, considerable increase in heart rate may occur without serious reduction of the amount of blood entering the ventricles during diastole. There is thus made possible a considerable increase of cardiac output per unit of time with increase in rate of contraction. With a rate beyond certain limits, however, the period of rapid filling is incroached on and the output falls. This is evident clinically in cases of paroxysmal tachycardia in which the rhythm is regular and each beat may be of an entirely normal character, but owing to the very rapid heart rate, the output per unit of time is decreased. The systolic arterial pressure falls and the venous pressure rises <sup>2</sup>. This change is also evident by the venous engorgement (cyanosis, liver enlargement, laryngeal edema, etc) which may occur in prolonged attacks

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\*From the Department of Physiology of the University of Wisconsin

1 Henderson. *Am J Physiol* **16** 325, 1906

2 Hooker and Eyster. *Bull Johns Hopkins Hosp* **19** 274, 1908



Of greater importance in their relation to cardiac disease in general, however, are those more severe and less transitory affections which involve not only the rate, but also the coordination of the beat, and which are usually, but not always, accompanied and preceded by valvular disease and more or less myocardial injury. These comprise extrasystoles, auricular flutter and fibrillation, partial heart block, and idioventricular rhythm in complete auriculoventricular dissociation. In partial dissociation, the reduction in ventricular efficiency is due merely to the slow ventricular rate. Auricular fibrillation is equivalent to auricular paralysis, so far as the pumping action of the auricles is concerned, and the decrease in pumping capacity of the ventricles is due, at least in part, to their increased rate.

Another factor seems to play a rôle in this case, however, namely, the prematurity of many of the ventricular beats, as will be discussed later in more detail. The other types involve disturbances in the coordination between auricular and ventricular contraction. The rôle that the auricular contractions play in the normal rhythm in filling the mammalian ventricle has been investigated by Henderson,<sup>1</sup> Straub<sup>3</sup> and Gesell.<sup>4</sup> The last mentioned investigator differentiated between the influence of the absence of auricular contraction and the influence of interference produced by auricular contractions occurring incoordinated with ventricular systoles. The methods were, first, abolition of auricular contractions by producing auricular fibrillation, and second, the influence of auricular systoles in their time relations to ventricular systole during experimental complete heart block with a ventricular rate maintained by rhythmic stimulation. The criterion used was mean arterial blood pressure. Gesell obtained changes in blood pressure amounting to 55 per cent of the pressure in the absence of auricular contractions by gradually shifting the time relations of auricular contractions with respect to ventricular contractions. With an independent ventricular rate, abolition of the auricular contraction causes a reduction of arterial pressure amounting to from 10 to 15 per cent. It is, therefore, evident that disturbances in cardiac rhythm, involving absence or incoordination of the auricular contractions, must involve a reduction in the pumping efficiency of the heart.

In recent years there has been much interest in abnormal cardiac rhythms. This interest has been mainly, however, in reference to their causes, diagnosis, prognosis and relation to other cardiac conditions. So far as we have been able to find, there has been only one study made as to their mechanical effect on the circulation, and this

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3 Straub J Physiol **11** 378, 1910

4 Gesell Am J Physiol **29** 36, 1911

only in reference to one type of abnormal rhythm. Lewis<sup>5</sup> studied the influence of auricular fibrillation on cardiac output, mean arterial pressure and venous pressure in cats and dogs. He found a decreased cardiac output, with usually a fall of arterial and rise of venous pressure, and ascribed the change entirely to the abnormal ventricular rate.

The experiments described in the present work were undertaken to determine under experimental conditions the influence on the pumping efficiency of the heart of the various types of abnormal cardiac rhythms that occur clinically. The abnormal rhythms studied were frequent ectopic beats, auricular flutter and fibrillation and partial and complete auriculoventricular dissociation.

#### METHODS

Dogs were used exclusively. The animals were etherized and the thorax opened under artificial respiration. The ventricular output was measured by means of a plethysmograph connected with a balanced piston recorder. Mean arterial pressure from the femoral artery was recorded by a mercury manometer. Ectopic beats (extrasystoles) were produced by induction shocks applied to the auricles and ventricles during early diastole at rhythmic intervals (after every fourth or eighth normal beat) by means of the stimulus selector described by Hirschfelder and Eyster.<sup>6</sup> Auricular flutter and fibrillation were induced by faradic stimulation of the right auricle, and auriculoventricular heart block was produced by heating the region of the auriculoventricular node and upper part of the bundle by a thermode applied through the right auricular appendage.

#### EXPERIMENTAL RESULTS

*Extrasystoles*—So far as the mechanical efficiency of the heart is concerned, it is important to consider that an extrasystole is practically always a premature beat, or occurs at a shorter interval of time after the preceding normal beat than usual, and that it is followed by a compensatory pause. Owing to the fact that it is premature, with a reduced diastole period during which the ventricle receives its complement of blood, it is a more or less deficient beat as compared to the normal. With extrasystoles we have, therefore, the replacement of a certain number of normal cardiac systoles by less efficient contractions.

The influence of auricular extrasystoles every fourth, eighth and sixteenth beat on cardiac output and arterial pressure is summarized in Table 2. The average effect was somewhat greater the more frequent the extrasystoles, but in most cases was relatively small and in

<sup>5</sup> Lewis. J. Exper. M. **16** 395, 1912.

certain individual cases probably within the normal variations of cardiac output. In several instances there was a slight increase above the normal, probably again within normal variations of output.

TABLE 1—EXAMPLES OF TYPICAL EXPERIMENTS

Character of Rhythm	Auricular Rate	Ventricular Rate	Ventricular Output per Minute	Percentage Decrease	Mean Arterial Pressure	Percentage Decrease
Normal	168	168	2020.8		106	
Auricular fibrillation		180	798.48	79.6	68	35.2
Normal	168	168	2252.88		102	
Normal	186	186	1217.66		60	
Auricular flutter	348	174	926.50	34.9	49	18.0
Normal	180	180	1197.72		60	
Normal	138	138	1881.6		70	
Auriculoventricular heart beat 2:1	144	72	1144.08	39.2	44	37.1
Normal	132	132	2079.84		76	
Normal	138	138	1881.6		70	
Auriculoventricular heart beat complete	126	36	652.2	65.3	46	34.3

TABLE 2—SUMMARY OF ALL EXPERIMENTS

Character of Rhythm	No. of Observations	Percentage Decrease in Cardiac Output		Percentage Fall in Blood Pressure	
		Average	Variations	Average	Variations
Extra systoles every 4th to 8th beat	8	6.9	+3.7 to -11.2	0	
Extra systoles every 16th beat	2	0		0	
Auricular flutter	15	15.6	+8 to -34.9	15.2	+8 to -40
Auricular fibrillation	7	40.6	15.2 to 79.6	34.8	25 to 55
Auriculoventricular heart block, partial (2:1)	4	44.0	39.2 to 50	33.0	30 to 37.1
Auriculoventricular heart block, complete	13	60.6	58.4 to 65.3	39.4	26.3 to 52

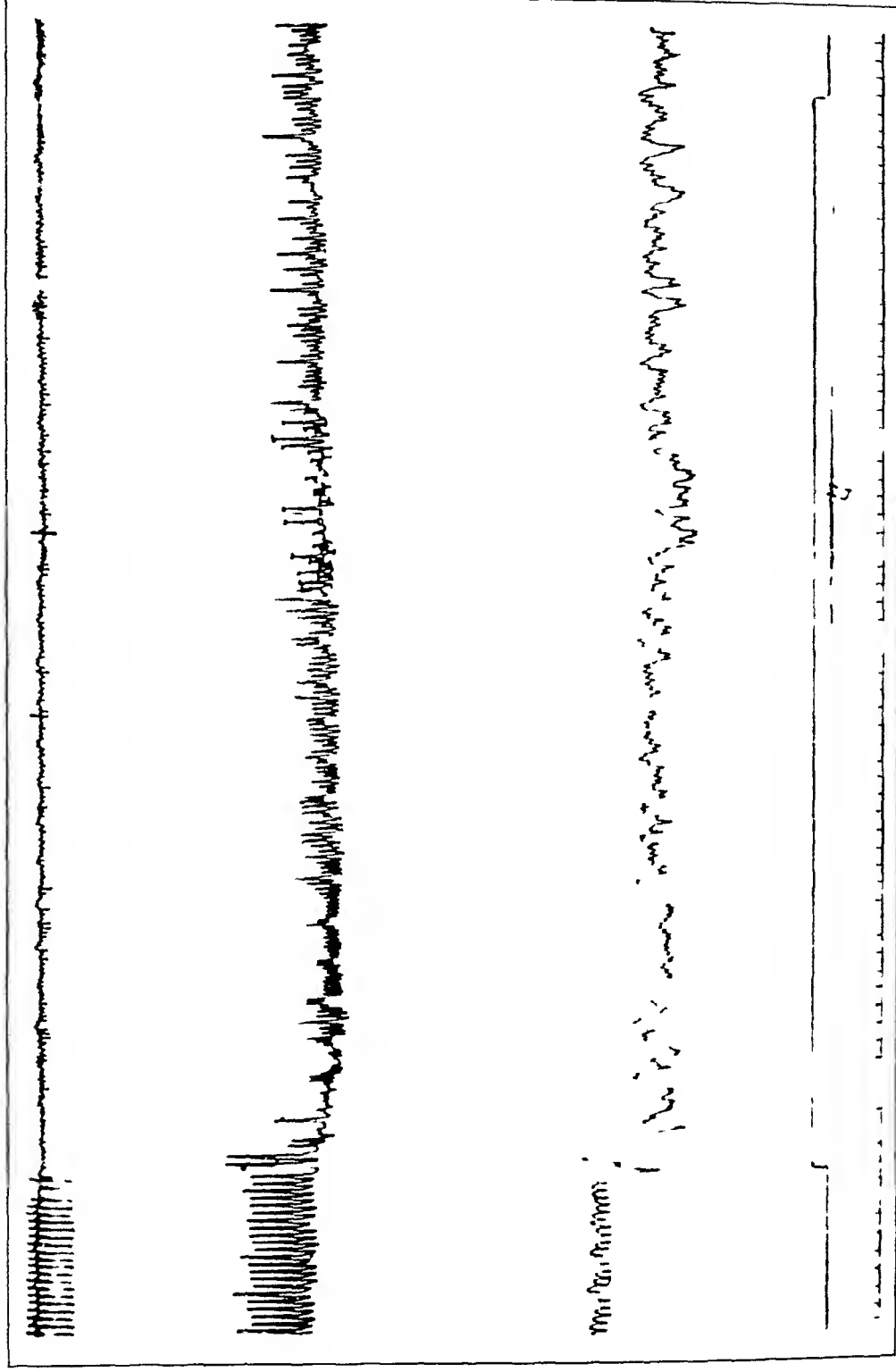
Theoretically, the degree of mechanical influence of extrasystoles would depend upon their number and on their prematurity. Furthermore, ventricular extrasystoles, because of the absence of or interference with auricular contraction and possibly because of atypical ventricular systoles, would be expected to produce a somewhat greater mechanical influence than an equal number of auricular extrasystoles. Attempts were made to obtain the same incidence of the extrasystoles in the different experiments, but we have not studied variation of incidence, nor have we combined ventricular with auricular extrasystoles.

*Auricular Flutter and Fibrillation*—Stimulation of the right auricle by rapidly increasing induction shock leads, as is well known, to flutter or fibrillation of the auricle. The former type of rhythm is characterized by a very rapid but coordinated contraction of the auricle, in the latter coordinated auricular beats are replaced by incoordinated segmental contractions of different muscular bundles of the dilated auricle.

and the condition is equivalent to auricular paralysis. In either case the ventricle follows the abnormal auricular rhythm in an irregular manner and shows both irregularity in rhythm and in size of contraction. (totally irregular pulse or *pulsus irregularis perpetuus*) Aside from the rapid ventricular rate, many of the beats are quite premature in character, and these not infrequently occur in a series of several ventricular beats followed by pauses which may be even longer than normal cycles. Especially in auricular fibrillation, many of the ventricular beats are so premature that the intraventricular pressure does not rise sufficiently to open the semilunar valves, and from the pumping standpoint are therefore totally inefficient. Experimentally, one may secure auricular tachycardia, flutter and fibrillation in most experiments by successively increasing the rate of auricular stimulation. With a rate of stimulation less than 250 per minute, each auricular contraction is usually followed by a ventricular contraction in the usual manner. Increasing the rate of stimulation may lead to an auriculo-ventricular heart block with the auricles beating twice as fast as the ventricles, or more frequently the impulses are conducted irregularly to the ventricles and an irregular ventricular rhythm occurs. Increasing the rate, especially if also the strength of the stimulus is increased, leads usually to auricular fibrillation, with, as a rule, an increased irregularity of ventricular contractions.

The experimental results of auricular flutter on cardiac output show considerable variation in the different trials. In a few there was actual increase in output, but the majority showed a decrease, reaching a maximum of 34.9 per cent. of the normal, as shown in the accompanying illustration. In the former, the ventricular rates were usually, but not always, lower than when a decrease occurred. The factors that should be considered as entering into the production of a decreased ventricular output in auricular flutter are (1) the degree of increase of ventricular rate, (2) the proportion of premature ventricular beats, and (3) the interference effects produced on ventricular fillings by the auricular systoles. Variations in the operation of these different factors no doubt explain the difference in degree of decrease of output produced.

Auricular fibrillation consistently decreased cardiac output, and the effect was in most cases much greater than in auricular flutter. It is important to note that this was not the result of a more rapid ventricular rate in fibrillation than in flutter, and to explain the greater effect in the former we must assume a larger proportion of premature and abortive beats or ascribe an important difference in the influence that auricular tachysystole and auricular paralysis exert on ventricular filling. The larger proportion of abortive ventricular beats in auricular



Experimental auricular fibrillation The top record records the contraction of the right auricle The second record is made by a ventricular cardiometer, the downstroke representing systole The third record is mean arterial blood pressure from the femoral artery The fourth and fifth records are those of the signal pen and time marker (one second intervals), respectively During the period marked by the signal pen, auricular fibrillation was induced by faradic stimulation of the right auricular appendage The record is to be read from left to right

fibrillation is usually very evident on inspection of the tracings, but why impulse conduction to the ventricle in auricular fibrillation should be more irregular than in auricular flutter is not entirely clear

There are probably at least three factors acting in auricular flutter and fibrillation to decrease ventricular output (1) an increase in ventricular rate beyond the optimum, (2) the presence of a variable number of premature and abortive beats, and (3) auricular interference or paralysis. That the first factor is not the sole one is shown by the fact that the decrease in output is not proportionate to the increase in ventricular rate

Study of the tracings would seem to indicate that the main factor is ventricular irregularity and the presence of abortive and premature ventricular systoles. Auricular fibrillation is characterized particularly by the large proportion of inefficient ventricular beats (pulse deficiency). The third factor, auricular interference in flutter and auricular paralysis in fibrillation, must also play a considerable rôle. This influence is exerted on ventricular filling and probably has a different proportionate influence with different ventricular rates. A more rapid auricular rate in flutter would presumably tend to increase the probability of interference

*Auricular Ventricular Heartblock* — In partial heartblock, the decrease in mechanical efficiency is due entirely to the slow ventricular rate. In complete block, an additional factor has to be considered, namely, the absence of the normal influence of the auricular contraction on ventricular filling. Some of the auricular contractions must be so placed as to actually produce interference with filling. Due to the slow ventricular rate in each case, it is found, however, that the filling is probably more complete than normal, since the output per beat is actually greater than in normal rhythm. The decrease in minute volume output is, therefore, due to the slow rate of contraction of the ventricle. In both partial and complete auriculoventricular block the reduction in volume output was approximately proportional to the percentage reduction in the ventricular rate. The effect was greater in partial block and the former shows the greatest average reduction of any of the abnormal types of cardiac rhythm

*Changes in Mean Arterial Pressure* — With a moderate degree of decrease in output, there is an approximately proportionate fall in mean blood pressure. When the output is markedly decreased, as in auricular fibrillation and heartblock, the fall in pressure is frequently considerably less than the decrease in output, indicating the occurrence of compensatory factors

## CONCLUSIONS

1 Frequent extrasystoles (occurring every fourth to eighth cycle) occurring in an otherwise normal cardiac rhythm have little influence in reducing the mechanical efficiency of the heart

2 Auricular flutter and fibrillation produce a variable reduction in the volume output of blood from the ventricles, depending on the degree of development of the abnormal rhythm The effect in fibrillation is greater than in flutter, and is mainly due to the irregularity of the ventricle and to the high percentage of premature and abortive ventricular beats, rather than to the fast ventricular rate

3 Partial and complete auriculoventricular dissociation produce a marked reduction in ventricular output, due to the abnormally slow ventricular rate In complete dissociation the reduction in mechanical efficiency is usually greater than in any other type of abnormal rhythm

4 The mean arterial pressure tends to fall as the ventricular output is reduced, but not to the same degree as the output when this is much affected, indicating the occurrence of compensating factors tending to maintain an approximately normal arterial pressure

# ON THE PLATELET COUNT AND BLEEDING TIME IN DISEASES OF THE BLOOD \*

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The blood platelets, the third corpuscular element of the blood, have since the fundamental work of Bizzozero, been the object of many researches, the results of which, in brief, are the following

1 The platelets are a normal element of the blood of great importance for coagulation and thrombosis

2 The place of origin of these bodies is not known with absolute certainty, although most authors believe in Wright's theory, that traces their descent to the megakaryocytes of the bone marrow

3 The platelet count normally varies more than does the number of red and white cells

4 The platelet count is low in genuine, idiopathic purpura, and in certain diseases of the blood and infections (pernicious anemia and typhoid)

5 When the number of platelets falls below certain values, the symptoms of a hemorrhagic diathesis occur

The methods for counting the platelets hitherto published, all use blood from a skin prick and may be divided in two groups

1 Direct count in dilutions after the ordinary hemocytometric principle, but using special liquids (Hayem, Afanassiew, Wright, Kinnicutt, etc.)

2 Indirect count, in which the relation of platelets to erythrocytes is counted in a variable dilution with a fixing liquid, thus avoiding the use of pipettes (Kemp, Brodie and Russell Pratt, Fonio etc.)

Different authors have estimated the normal platelet count as between 200,000 and 800,000 per cmm all however, agreeing that the boundary lines of the normal must be placed rather widely apart

In 1918, Oluf Thomsen<sup>1</sup> introduced a new technic for the enumeration of the platelets which makes this procedure infinitely more reliable than previously

The technic in brief, is as follows <sup>2</sup>

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\* From the medical clinic of the Copenhagen University, Prof. Knud Faber

1 Hospitalstid 62 161 (Feb 5) 1919

2 The procedure described is slightly modified from the original method of Thomsen



In a 5 c c centrifuge tube, graduated in one-tenth c c, measure 0.5 c c of a 10 per cent sodium citrate solution. By venepuncture with a sharp, not too narrow, needle 4.5 c c of blood are run down into the citrate solution and mixed with it by corking and shaking. The blood adhering to the cork is wiped off with a piece of cloth or filter paper, and the tube is left to stand for about an hour.

In all cases, except severe polycythemia, the red blood cells, and most of the white blood cells, have been precipitated so as to leave a layer of turbid plasma *containing the platelets in a homogeneous and very stable suspension*, which does not undergo any change for at least five hours. A small quantity of this mixture is drawn off with an ordinary white blood cell melangeur, and diluted in the proportion of 1:20 with a solution containing 9 ‰ sodium chlorid and 2 ‰ liquor formaldehydi, possibly also a small quantity of brilliant cresyl blue to stain the platelets.

The technic of Ellermann and Erlandsen, necessitating the use of separate pipettes for "blood" and diluting fluid, is to be recommended (*Ugeskr f laeger*, No 6, 1912).

A drop of the plasma dilution is placed in the ordinary closed counting cell of Thoma (Burker's and other open models must not be used on account of the evaporation).

In the dilution, the platelets sediment readily, and may be counted after standing from one-half to one hour. The platelets show as small refractive bodies of a blue color at low focus.

By counting ten large squares and dividing the total with two, the number of platelets in thousands contained in 1 c mm of citrated plasma is found.

When the relation of citrated blood and the volume of the blood cells are known, the platelet count per c mm of blood may easily be calculated.

According to Oluf Thomsen, the precipitate, on centrifuging the blood for ten minutes at 2,000 revolutions per minute, still contains 5 per cent of plasma. This value I have found a little low, since centrifuging for fifteen minutes, at 3,000 revolution per minute, still leaves from 5 to 10 per cent of plasma among the cells.

In the determinations that I have carried out, the precipitate after one and one-half hour of centrifuging, which conforms very nearly with the hematocrit results, have been used as a measure for the bulk of the blood cells.

The calculation of the platelet count is then made from the following formula or by multiplying with a constant calculated for each value of the precipitate.

$$\text{Platelet count} = \frac{(\text{citrated blood} - \text{precipitate}) \times \text{platelets per c mm plasma}}{\text{Citrated blood} - \text{citrate}}$$

The error caused by an inaccurate determination of the cell volume is not large, as is shown by the following example

$$\text{Citratd blood} = \frac{0.5}{4.5} \begin{matrix} \text{(a) precipitate after 15 minutes' centrifuging 2 c c} \\ \text{(b) precipitate after 1\frac{1}{2} hours' centrifuging 18 c c} \end{matrix}$$

Counted 500,000 platelets per c mm citrated plasma

Platelet count calculated by  $\begin{matrix} \text{(a) 333,000 per c mm} \\ \text{(b) 355,000 per c mm} \end{matrix}$

The results of counts in double specimens and in the same plasma after varying times have convinced me of the reliability of the method. Within five hours from the taking of the blood there is no loss of platelets from sedimentation. In clean punctures, with good needles, the platelets never adhere to the other blood cells. Small bore needles, such as are used for hypodermic syringes, cause agglutination of the platelets, therefore, must never be used. The few leukocytes found in the counting cell must not show adhering platelets.

The research that I have carried out was made on mixed material, consisting of hospital patients in the wards of the Rigshospital and other Copenhagen hospitals.

Consequently, the difficulties in drawing the boundary lines of the normal may be somewhat greater, but the conclusions seem to me to be more valuable than those to be drawn from an examination of a necessarily smaller number of absolutely normal persons. In 122 individuals, with seemingly indifferent diseases, 179 examinations were made, and the platelet count varied between 200,000 and 500,000 per c mm of blood.

If we arrange these results in groups of 50,000 we find the following

TABLE 1—NORMAL PLATELET COUNTS

Platelet Count	Number of Examinations	Number of Persons
200,000-250,000	21	10
251,000-300,000	22	16
301,000-350,000	38	34
351,000-400,000	48	38
401,000-450,000	37	33
451,000-500,000	13	10
Total	179	122

The majority of the determinations show platelet counts between 300,000 and 450,000 per c mm.

Before giving the results of the platelet count in cases of blood disease, I would mention the fact that a slightly diminished number of platelets was found in one case of acromegaly, but not in two other

cases, and in one case of typhoid fever (third week), but not in two other cases (first and second week, respectively) Counts above 500,000 were found irregularly in the course of some acute infections

In accordance with other observers I found the platelet count normal in two cases of hereditary hemophilia and slightly elevated in a third case, showing a pronounced simple anemia

In one case of hemolytic icterus with blood alterations of the pernicious type, the plate count showed very low normal values, once even less than 200,000

TABLE 2—HEMOPHILIA

Number	Date	Platelets	Hemo- globin per Cent	Red Blood Cells, Millions	Color Index	White Blood Cells	Bleeding Time, Minutes
1	4/23	402,000	87	5 14	0 84	6,100	2
	5/27	457,000	91	5 19	0 88	7,200	3
2	5/27	394,000	93	5 24	0 89	6,400	8
3	6/26	528,000	69	4 65	0 66	9,100	
4	1918						3

TABLE 3—ICTERUS HEMOLYTICUS

Number	Date	Platelets	Hemo- globin per Cent	Red Blood Cells, Millions	Color Index	White Blood Cells	Bleeding Time, Minutes
1	5/31	213,000	44	1 99	1 11	6,200	3
	6/ 6	216,000					
	6/12	230,000	50	2 03	1 23	4,500	
	6/30	186,000	48	2 30	1 02	4,600	6

As simple anemias I have classed those cases in which the hemoglobin percentage was less than 70 (100 per cent hemoglobin = 18.5 per cent oxygen capacity), in which the colorimetric index was less than 1, and in which there were no signs of any other disease of the blood

In twenty-one such patients (six cases of cancer, seven of anemia due to hemorrhage, and eleven obscure simple anemias) I have carried out twenty-seven platelet enumerations

Thirteen determinations made in eleven patients were normal, rather high values, while fourteen determinations on ten patients showed increased counts The platelet counts observed in some cases were over 1 million per c mm

No constant relation between the platelet count and the cause or degree of the anemia could be traced, but, possibly, the result may be of some prognostic value, a high platelet-count indicating a better regenerative power of the bone marrow

The results in pernicious and pernicious aplastic anemia are shown in Table 4

Of the sixteen cases tabulated, fourteen were typical genuine pernicious anemia, while two (numbers 8 and 9) belonged to a more aplastic type. As the latter both died and the postmortem confirmed the diagnosis, I feel safe in ranging them in here.

TABLE 4—PERNICIOUS ANEMIA

Number	Date	Platelets	Hemo- globin per Cent	Red Blood Cells, Millions	Color Index	Bleeding Time, Minutes
1	12/29	144,000				
	1/ 9	107,000	76	3.20	1.18	
	1/24	128,000				
	2/15	140,000	67	3.30	1.01	
	3/15	181,000				5½
2	3/ 6	66,000				10
	3/11	61,000				9½
	3/21	74,000				9
	4/ 1	55,000				
	4/24	83,000	46	1.51	1.51	7
	5/14	95,000	47			5
	6/14	74,000	49	1.58	1.55	>10
	7/ 1—	37,000	32	1.19	1.34	>10
3	4/29	188,000	79	3.80	1.04	
4	5/24+	36,000	16(?)	0.86		>10
5	5/31	116,000	52	1.87	1.40	2½
	6/ 7	108,000	50	1.65	1.66	5
	6/14	90,000	56	1.90	1.47	
	6/21	173,000	63	2.02	1.56	
	6/28	177,000	73	2.49	1.49	3
	7/ 7	263,000	82	2.63	1.56	2½
6	7/ 4	116,000	45	1.45	1.55	
7	7/ 4+	16,000	15	0.71	1.05	>10
8	5/ 2+	34,000	14	0.61	1.15	>10
9	2/20	105,000	47	1.95	1.23	3½
	2/25+	40,000	35	1.43	1.22	7½
10	8/16	110,000	25	0.71	1.76	5
11	8/25	193,000	56	2.14	1.31	
	10/ 9	481,000	91	3.91	1.16	
12	8/30	246,000	45	1.90	1.19	3½
13	9/ 6	55,000	43	1.53	1.40	
	9/19	23,000	28	0.93	1.51	>10
14	9/29	56,000	31	0.95	1.63	>10
15	10/27	22,000	28	1.05	1.3	
	11/ 1	25,000	27	0.96	1.4	
16	10/22	13,000	21	0.57	1.8	
	10/30	16,000	16	0.42	1.9	

Evidently, in pernicious anemia one generally finds a diminished platelet count most pronounced in the grave cases (Cases 2, 4, 7, 8, 9, 13, 14, 15 and 16), less so in the milder cases and during remissions.

In two cases, when the hemoglobin and red blood cell values reached nearly the normal (Cases 5 and 11), the platelet count also became normal. In Case 12 there was a low normal platelet count, but this patient, whom I have not had the opportunity of studying further, was convalescing rapidly and was soon discharged.

The value of the study of the platelets in pernicious anemia rests on their importance for the differential diagnosis between simple anemias and those of Biermer's type, and furthermore on their value as a means of making a prognosis

Cases in which the platelet count has gone very much under 100,000 per c mm generally terminate fatally, while those with higher counts tend to remissions

Complications in diagnosis might arise in cases of simple anemia following genuine purpura, but this disease seems to be very rare in Denmark, since I have only observed one case in a child and that before beginning this series of observations

In leukemia the behavior of the platelets is more variable (Tables 5 and 6)

TABLE 5—MYELOID LEUKEMIA

Number	Date	Platelets	Hemo globin per Cent	Red Blood Cells, Millions	Color Index	White Blood Cells	Bleeding Time, Minutes
1	2/10	83,000	47	2 20	0 96	249,000	>10
	2/17	96,000				100,000	>10
	2/24	75,000					
	3/ 5	118,000					
	3/12	134,000				107,500	>10
2	5/30	362,000	26	1 15	1 12	40,100	2½
	6/ 6	302,000	21	1 04	1 00	32,600	3½
	6/16	247,000	18	0 85	1 03	19,700	3
3	4/23	771,000	70	4 30	0 81	181,700	2
	5/ 6	568,000	52	2 91	0 89	27,600	2
4	4/ 1	1,366,000	85	4 81	0 98	75 000	3
	4/ 7	1,291,000				66,200	2
5	9/24	403,000	58	4 20	0 70	22,500	

TABLE 6—LYMPHATIC LEUKEMIA

Number	Date	Platelets	Hemo globin per Cent	Red Blood Cells, Millions	Color Index	White Blood Cells	Bleeding Time, Minutes
1	12/30	173,000	82	3 94	1 05	15,600	
	1/16	127,000	90	4 10	1 09	6,000	5½
2	4/20	86,000	72	3 80	0 95	94,000	4
3	4/21	134,000	35	1 30	1 35	120,000	5½
4	3/29	170,000	78	4 35	1 15	247,000	2½
	4/ 7	175,000					2
	4/22	156,000	73	3 90	0 94	106,000	2
	5/ 5	137,000					3
	5/15	146,000				144,000	2
	6/ 3	132,000				125,000	2½
	6/21	139,000	66	3 60	0 92	63,100	
5	6/16	296,000	96	5 56	0 79	92,500	3
	6/17	287,000	97	5 42	0 89		
	7/ 2	314 000				108,400	4
6	4/22	48,000	59	3 10	0 95	2,200	
	4/28	48,000					>10
	5/13	36,000	56	3 07	0 91	2,400	
	5/26	49,000	51	2 66	0 96	3,200	>10
	6/17	58,000	60	3 11	0 96	1,800	
7	8/17	7,000	14	0 67	1 04	166,000	>10

In seven cases of lymphatic leukemia, the platelet count was low in six, but slightly so in three cases, considerably lower in the remaining three cases, one of which must be set apart on account of its showing at the time of the examination, a blood picture more like an aplastic anemia (Case 6)

In myeloid leukemia the results were even more divergent, inasmuch as one case showed a very low platelet count, two had normal values and two had a very considerable increase. It may be of importance to remark that the two first cases showed blood alterations resembling those of pernicious anemia.

Inasmuch as these variations are inconstant, one cannot attribute any diagnostic value to them, and the platelet count in leukemia only serves to direct our attention to an impending hemorrhagic diathesis.

The reason for the low counts in leukemia is obscure. It cannot be explained by the roentgen-ray treatment used, as three of the six patients with lowered platelet count never had been treated before, and two of the five patients with normal or increased values had been treated previously, also, the platelet count showed no drop during an effective roentgen-ray treatment.

In many of the cases mentioned the platelet count was low without any signs of hemorrhagic diathesis appearing. In order to bring a latent tendency to hemorrhage to light, I have carried out a large number of bleeding time determinations by Duke's method. The blood from a small skin prick (2 mm deep) was wiped off every one-thirtieth second till the bleeding stopped. I found the normal bleeding time in about 100 determinations to lie between one and one-half and four minutes.

In Tables 1 to 6 the bleeding time is found on the extreme right.

In the only case of hemolytic icterus examined (Table 2) the bleeding time at first was normal, but became slightly lengthened, when the platelet count dropped to 186,000 per c mm.

From Tables 4, 5 and 6 it appears that the bleeding time may be moderately prolonged when the number of platelets lies between 100,000 and 200,000, e g, in pernicious anemia (Case 1), where a platelet count of 181,000 occurred, together with a bleeding time of five and one-half minutes. The lower the number of platelets falls, the more likely one is to find a definitely long bleeding time. In a single case (lymphatic leukemia, Case 2) the bleeding time was normal (four minutes), although the platelet count was 86,000.

In all other cases where the platelet count fell below 100,000 per c mm, one finds a protracted bleeding time, often longer than ten minutes.

In three out of four cases of hemophilia with a normal platelet count, the bleeding time also does not exceed the average limits. In a fourth case it is somewhat lengthened. In all cases of simple anemia the bleeding time was normal, even rather shorter than normal.

#### SUMMARY

1 The method of Oluf Thomsen for counting the platelets in citrated plasma is described.

It gives reliable results. At the same time it permits a determination of the prothrombin time with a slight alteration of the technic of Howell, also a determination of the fibrin percentage according to an unpublished method elaborated by the author, thus making possible a systematic examination for hemorrhagic diathesis on a single blood specimen.

2 The number of platelets in normal individuals lies between 200,000 and 500,000<sup>4</sup>.

3 The platelets are diminished in number in pernicious anemia, in most cases of lymphatic leukemia and in some cases of myeloid leukemia. Normal values are found in hemophilia, and augmented values are found in many cases of simple anemia and some of myeloid leukemia.

4 The diagnostic and prognostic importance of the platelet count in diseases of the blood is discussed.

5 The bleeding time determination of Duke helps to disclose a latent hemorrhagic diathesis due to platelet deficiency, as symptoms may not appear without a provocative cause. It is shown that platelet counts of less than 100,000 per c mm generally cause a tendency to bleed.

6 The counting of the platelets and determination of the bleeding time is of extreme importance as a pre-operative measure, especially in cases of aplastic anemia, in which an operation often is performed for explorative purposes, occult cancer being suspected.

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<sup>4</sup> In absolutely normal persons the number of platelets rarely is less than 300,000 per c mm.

## Book Review

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TOTAL DIETARY REGULATION IN THE TREATMENT OF DIABETES By Frederick M Allen, M D, Edgar Stillman, M D, and Reginald Fitz, M D Monographs of the Rockefeller Institute for Medical Research, No 11, Oct 15, 1919 The Rockefeller Institute for Medical Research, New York

The monograph opens with a history of diabetes written from the standpoint of treatment which, with bibliography, fills seventy-eight pages. It is stated in the preface that it was written as the opening chapter of a treatise in three parts, and that it was to have been followed by chapters which do not appear in the present volume. The latter, according to the original plan, would have been published in a separate section. The history is followed by a detailed exposition of the management of diabetic patients as carried out in the Rockefeller Institute. Following this there are 284 closely printed pages and numerous charts devoted to the clinical records in full of seventy-five cases of diabetes treated at the same institution. The remainder of the volume contains chapters on phases of the problem which Allen and his co-workers have made the subject of special investigation, thus a chapter on pancreas feeding, a chapter on exercise, and one on the influence of fat in the diet. These are followed by a discussion of results and prognosis, and a chapter on etiology and pathology.

One familiar with the literature of diabetes, including especially the previously published works of Allen and Joslin, will find in the volume little that is strictly new. The detailed case records have not been published before, and they form an important feature, but apart from these, the work is largely a restatement of the work and views of Allen and his co-workers.

The historical part indicates that previous writers had established the principle of making the diabetic patient sugar-free and of keeping him consistently sugar-free thereafter, whenever this was possible. It had been accomplished in cases sufficiently mild by restricting the carbohydrate alone. In a less mild group of cases it had been accomplished by restricting the protein as well as the carbohydrate. It was known that even in the most severe cases fasting, sufficiently prolonged, would result in the disappearance of all symptoms of diabetes, provided there were no preventing intercurrent disease. It was not realized that the severest cases, or even the moderately severe cases, could be kept consistently free of symptoms of diabetes for an indefinite period of time after they were desugarized by fasting. Fear of the effects of continued under-nutrition of the degree and kind thought necessary had led to the practice of increasing the diet too rapidly and too much, so that symptoms promptly returned. Allen desugarized all, or nearly all, patients by an introductory fast and subsequently refrained from adding food beyond the limits of the patient's power to assimilate it. He thus extended the principle of desugarizing and keeping the patient consistently sugar free to a large group of cases for whom this had not been considered feasible. In so doing he discovered new possibilities in the line of restoration of tolerance and the conversion of the more severe into the less severe or milder types of diabetes. The gradual addition of measured quantities of carbohydrate, protein and fat to desugarized diabetic patients who proclaim the limit of their assimilative powers by excreting abnormal quantities of sugar or acid proved a good method for studying the



metabolic effects of the foodstuffs individually and collectively. This method, applied with the facilities of the Rockefeller Institute, has led to a much clearer concept of the principles underlying the dietetic management of diabetes than had been held before. Total dietary regulation and the deleterious effects of an undue quantity of fat in the diet are emphasized throughout the work.

The book is written somewhat in the form of a diary, in that views and cases are presented in their entirety in the order of their arrival. It contains much valuable data which would be more easily accessible if it were classified, indexed and separated from the nonessential, but it tells the story of an advance in the dietetic management of diabetes that has resulted in a decrease of suffering and a prolongation of life. It is a work which should be read by all those who assume responsibility for the care of diabetic patients.

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Fifty cents each will be paid for the following issues of the Archives of Internal Medicine: January, March, June, August, 1918; January and July, 1916; November, 1915; January, 1911; July, 1909. AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.

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## STUDIES ON ARTHRITIS IN THE ARMY BASED ON FOUR HUNDRED CASES

### IV STUDIES IN THE RELATION OF CREATIN METABOLISM TO ARTHIRITIS

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The researches of the past fifteen years on the chemistry and biochemistry of creatin and creatinin have abundantly established the high importance of these substances in the animal economy, and it seems appropriate at the outset of this paper to present a brief summary of those investigations which have a direct bearing on the subject here considered

Previous to 1906, general acceptance was given to the theory of the older investigators<sup>1</sup> that the creatinin eliminated in the urine is a waste product derived from muscle creatin. In 1906 Folin published the results of experiments<sup>2</sup> in which he showed that ingestion of creatin did not cause the appearance of creatin in the urine, and did not appreciably influence the elimination of creatinin, from which he concluded that though chemically closely akin, creatin and creatinin are biologically distinct. Since that time numerous observers have confirmed these experiments (Klercker, Wolf, Shaffer) and the metabolic gap between the two substances has grown increasingly wider<sup>3</sup>. Meyers and Fine,<sup>4</sup> on the other hand, have carried out extensive experimental work designed to substantiate the theory that muscle creatin is the

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1 Van Hoogenhuyze and Verploegh. *Ztschr f Physiol Chem* 46 416, 1906, Jaffe. *Ibid* 48 430, 1906

2 Folin. *Hammarsten Festschrift*, 1906

3 It seems difficult to accept any definite conclusions regarding the normal fate of creatin in the body from experiments in which massive doses (20 gm) of creatin are fed and small (from 0.30 to 0.49 gm) quantities of creatin are recovered from the urine. Rose and Dimmitt. *J Biol Chem* 26 346, 1916

4 Meyers and Fine. *J Biol Chem* 14 18, 1913

precursor of the creatinin eliminated in the urine. They have called attention especially to the close parallelism between the average creatin content of the muscle of a given species and the creatinin coefficient for that species (Mg of creatinin nitrogen per twenty-four hours per kilogram of body weight). Such data are highly suggestive, but it is difficult to draw incontestable conclusions from this parallelism. In the first place, it is doubtful whether any creatin is set free from the muscles under normal circumstances.<sup>5</sup> Moreover, Folin and Buckman<sup>6</sup> have shown that the creatin content of the muscles of animals of a given species varies within too wide limits to permit of average figures being used in calculation. Finally, as pointed out by Benedict and Osterberg,<sup>7</sup> and Folin and Denis,<sup>8</sup> the creatinin coefficient is a very variable quantity when applied to *different* individuals, owing to the fact that other tissues, notably adipose tissue, not directly concerned with the production of creatinin, influence to a large extent the weight of an animal. At present, then, it would seem that there is no undisputed evidence to show that creatin is, under any conditions so far studied, a precursor of any important part of the creatinin eliminated.

Regarding the significance of urinary creatin, it has been known since the work of Folin in 1905,<sup>9</sup> that the amount of creatinin eliminated on a creatinin-free diet is a constant for a given individual, and is independent of the amount of protein ingested—thus suggesting that the creatinin eliminated is an index of the endogenous or cellular metabolism. The significance of urinary creatinin has been studied by numerous investigators since then, among them Taylor and Rose,<sup>10</sup> Fowler and Hawk,<sup>11</sup> Shaffer,<sup>12</sup> and Meyers and Fine,<sup>13</sup> and the consensus of opinion seems to be that the urinary creatinin represents an end-product of a normal (endogenous) metabolic process taking place chiefly in the muscles, and that the amount eliminated is proportional to the active mass of muscle tissue present (on a creatinin-free diet).

Creatin, as is well known, does not occur, or occurs only in very small traces, in the urine of normal adult males on an ordinary diet. Its occurrence in a great variety of pathologic conditions and conditions of altered metabolism (fevers, starvation, carcinomatosis, acidosis, faulty carbohydrate utilization, high protein feeding, child-

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5 Folin and Denis. *Ibid* **17** 493, 1914

6 Folin and Buckman. *Ibid* **17** 183, 1914

7 Benedict, S. R., and Osterberg, E. *J Biol Chem* **18** 195, 1914

8 Folin and Denis. *Loc Cit*

9 Folin. *Am J Physiol* **13** 118, 1905

10 Taylor and Rose. *J Biol Chem* **14** 419, 1913

11 Fowler and Hawk. *J Exper M* **12** 388, 1910

12 Shaffer. Quoted by Hawk, *Pract Physiol Chem* 1918, p. 490

13 Meyers and Fine. *J Biol Chem* **14** 388, 1913

hood, pregnancy, massive doses of creatin) has formed the basis of a large number of reasearches regarding the origin of creatin and its relation to creatinin

There are several hypotheses advanced to account for the appearance of creatin in the urine in various conditions F B Benedict,<sup>14</sup> who was the first to report creatinuria in starving men, suggested that the creatin is derived from muscle creatin This problem has been further studied by Mendel and Rose,<sup>15</sup> and by Myers and Fine,<sup>16</sup> and the latter observers concluded from their experiments that the creatin of the urine in starvation owes its origin to the disintegration of muscle tissue But, as Benedict (S R) and Osterberg<sup>17</sup> suggest, disintegration of muscle tissue may mean either a selective liberation of creatin or a more or less complete destruction of the proteins of the tissue From the experiments of Folin and Denis,<sup>18</sup> it is difficult to see how any selective liberation of creatin can occur The last named investigators showed from observations on the absorption of creatin from the blood by living muscle, that living muscle contains practically no creatin, and concluded "that the creatin found on analysis is a post-mortem product originally constituting a part of the living protoplasm" On the other hand, as pointed out by Benedict and Osterberg, if an actual destruction of muscle protoplasm does occur, and the creatin is split off as such during the process of destruction, we should expect that the total nitrogen of the urine would closely parallel the creatin eliminated (or creatin plus creatinin) These experiments<sup>19</sup> showed, however, that a high creatin elimination could be maintained which was independent of the tissue destroyed Benedict and Osterberg worked with completely phlorizinized dogs, sparing the body proteins by feeding the necessary amount of creatin-free protein The animals were fasted for a preliminary period of two or three days before the injections of phlorizin were begun, and in some cases the fasting was continued after the injections of phlorizin had been begun That is, the animals were first subjected to simple starvation, then to greatly "intensified starvation" (phlorizin), and were then kept in nitrogen equilibrium (or nearly so) by feeding creatin-free protein to spare the body proteins The creatin elimination, slight during simple fasting, increased markedly on administration of phlorizin (intensified starvation) and then showed a decline, unless an adequate supply of protein was furnished, but throughout was independent of the body

14 Benedict, F G Carnegie Institute Washington, Pub 77, 1907, p 386

15 Mendel and Rose J Biol Chem **10** 213, 1911

16 Meyers and Fine Ibid **15** 283, 1913

17 Benedict, S R, and Osterberg, E J Biol Chem **18** 195, 1914

18 Folin and Denis Ibid **17** 493, 1914

19 Benedict and Osterberg Loc Cit

TABLE 1—RESULTS OF ANALYSES OF NORMAL CONTROLS AND ARTHRITIS PATIENTS

Cnsc	Name	Regis- tration No	Urine, Gm per 24 Hours						Blood, Mg per 100 C c			Remarks	
			Age	Weight	Date	Creat- inin	Mg Creat- inin per Kg	Total Nitrogen	Percent age Nitrogen as Creat- inin	Total Non- protein Nitrogen	Creat- inin		
Control	Cnif	1	22	68.5	3/16	0.0	1.40	7.6	8.21	6.3	26.0	3.7	Normal man
	Huds	2	24	84.0	3/16	0.0	1.72	7.5	6.42	10.0	27.4	4.2	Normal man
	Ldde	3	25	65.0	3/16	0.0	1.65	9.4	7.26	8.4	28.2	4.8	Normal man
	Buck	4	27	62.3	5/10	0.0	1.45	8.7	9.98	5.5	30.7	4.6	Normal man
	Bell	5	24	74.2	5/10	0.0	2.18	11.0	10.20	7.9	28.8	3.7	Normal man
	Fiel	6	25	63.7	5/12	0.0	1.85	10.6	9.18	7.3	29.0	4.6	Normal man
	Fdw	7	22	62.0	5/12	0.0	1.60	9.5	10.82	7.9	27.8	4.0	Normal man
	Stuek	8	26	61.0	5/15	0.0	1.35	8.3	7.80	6.5	25.3	4.5	Normal man
	Boda	9	23	57.7	5/15	0.0	1.01	6.5	7.20	5.3	30.9	5.0	Normal man
	Averages		24	66.5		0.0	1.58	8.8	8.53	7.26	28.4	4.3	10
64	Fish	3689	23	62.0	5/ 1	0.0	1.25	6.9	6.87	6.8	30.9	2.9	Convalescent, ambulatory
65	Gal	5245	28	65.0	3/ 4	0.0	1.38	7.8	7.90	6.5	23.0	3.4	Convalescent, ambulatory
66	Bass	3888	21	61.3	5/ 2	0.0	0.93	5.1	6.58	5.2	29.5	3.5	Chronic tonsillitis tuberculous arthritis
67	Burg	3556	23	62.3	4/28	0.48*	1.28	7.7	12.32	3.9	19.5	3.6	Convalescent, ambulatory
68	Turn	3982	31	75.0	4/29	0.0	1.90	9.4	16.24	4.4	22.2	3.7	Convalescent, ambulatory
48	Jans	4238	32	58.2	5/ 5	0.0	1.37	8.7	8.15	6.2	30.8	3.9	Convalescent, ambulatory
69	Meint	4481	21	63.5	4/ 1	0.0	1.62	9.5	11.32	5.3	28.2	4.0	Convalescent, ambulatory
6	Hay	1699	20	54.8	5/ 3	0.0	0.90	6.2	6.69	5.0	24.0	4.0	Convalescent, ambulatory
70	Font	3809	20	58.0	5/ 7	0.0	1.16	7.2	9.76	4.3	28.8	4.0	Tuberculous spine (?)
46	Heth	4257	40	85.0	5/11	0.0	1.44	6.3	10.21	5.6	27.4	4.1	Convalescent, ambulatory
71	Craw	4567	30	54.6	4/29	0.0	1.31	9.4	7.42	6.6	20.2	4.2	Severe, chronic, bed
72	Bark	4653	27	61.3	5/ 2	0.0	1.37	6.1	8.34	6.2	28.3	4.2	Chronic otitis media, (?) tuberculous pleural and pericardial adhesions, ulcers of leg

52	Lyn	4836	32	61.5	5/13	0.0	1.30	7.9	6.16	7.9	26.5	4.4	0.8	Convalescent, ambulatory
73	Jor	5294	20	63.5	5/1	0.0	1.48	7.7	9.00	6.1	30.6	4.4	0.9	Convalescent, ambulatory
74	Cur	5351	32	56.3	5/9	0.0	2.08	13.3	7.74	0.8	23.5	4.4	0.9	Convalescent, ambulatory
75	Dro	4828	30	66.8	4/22	0.0	1.41	7.3	8.20	0.3	25.7	4.5	1.0	Convalescent, ambulatory
76	Hick	1803	47	71.5	5/14	0.0	1.60	5.4	6.47	6.3	25.5	4.5	1.0	Convalescent, ambulatory
77	Rob	5051	26	78.7	4/30	0.0	1.46	6.6	5.72	9.4	10.8	4.7	1.4	Convalescent, ambulatory
78	Flin	5252	27	68.3	4/12	0.0	1.22	6.6	7.61	8.0	25.1	4.8	1.1	Convalescent, ambulatory
79	Morr	5143	26	63.8	5/11	0.0	1.15	6.5	7.37	4.1	24.8	4.8	1.0	Convalescent, ambulatory
80	Fol	4919	24	64.2	4/22	0.0	1.71	10.6	12.83	4.5	30.9	4.9	1.0	Convalescent, ambulatory
81	Cott	4-11	34	70.3	4/18	0.0	1.80	9.2	11.21	6.0	27.9	4.9	1.3	Convalescent, ambulatory
82	Kirk	4997	23	59.2	5/5	0.0	1.53	6.7	10.00	5.7	27.4	4.9	1.4	Convalescent, ambulatory
83	Herr	4257	40	83.0	4/2	0.0	2.65	11.7	12.52	8.0	28.2	5.0	1.8	Convalescent, ambulatory
84	Wass	3658	21	60.0	4/7	0.0	1.06	6.6	6.78	5.9	29.0	5.0	1.5	Severe, chronic, bed
85	Jeff	1525	24	55.4	3/27	0.0	1.33	9.2	6.73	7.7	28.2	5.0	1.8	Chronic, level, ambulatory
86	McKen	4973	20	57.0	4/30	0.0	1.82	12.0	8.18	8.3	28.5	5.0	1.2	Acute attack, bed, febrile
87	Cox	2477	36	65.5	4/13	0.0	1.63	9.3	7.12	8.5	28.3	5.2	1.3	Convalescent, ambulatory
88	Chan	4040	20	68.2	5/8	0.0	0.89	4.8	10.80	3.0	24.9	5.2	0.8	Convalescent, ambulatory
89	Herr	4501	24	67.1	4/20	0.0	1.70	9.3	6.07	10.3	22.1	5.4	1.4	Acute attack, bed
90	Mill	5313	22	53.6	5/13	0.0	1.36	8.9	10.82	4.7	30.7	5.4	0.9	Convalescent, ambulatory
91	Mait	4905	15	82.0	3/26	0.0	0.91	4.2	4.65	7.3	45.1	5.5	0.7	Chronic, severe, bed
92	Hin	2503	25	56.4	4/14	0.0	1.42	9.2	5.80	9.0	31.9	5.5	1.4	Convalescent, ambulatory
93	Sput	4479	32	78.3	5/3	0.0	0.79	3.7	5.08	5.6	26.3	5.7	1.0	Tuberculous arthritis (?)
94	Obc	3712	24	61.2	5/14	0.0	1.15	9.0	8.70	6.1	26.3	5.7	1.0	Convalescent, ambulatory
95	Kotsc	3899	25	56.0	3/31	0.0	1.52	8.8	11.00	5.1	28.6	5.8	0.8	Chronic, severe, bed
96	Hin	4836	22	61.5	4/17	0.0	1.03	6.3	7.58	7.4	30.9	5.9	1.1	Convalescent, ambulatory
97	Tan	4238	32	59.5	4/7	0.0	1.86	11.6	6.46	8.4	26.2	6.0	1.3	Convalescent, ambulatory
98	Kal	5313	42	71.8	5/9	0.0	1.30	9.7	9.16	10.8	24.1	6.6	0.8	Acute attack, febrile
99	Low	3539	42	72.3	4/7	0.1	1.46	7.7	7.23	7.5	29.1	6.8	1.1	Chronic, ambulatory
100	Lang	4670	21	57.3	4/12	0.0	0.86	5.6	6.26	8.9	30.0	7.0	0.7	Chronic, ambulatory
101	Chan	4049	26	69.2	4/14	0.1	1.76	9.4	10.45	7.8	38.5	7.0	0.9	Chronic, ambulatory
102	Chan	4049	26	67.0	4/20	0.40	1.06	5.8	6.90	5.6	34.5	7.0	1.5	Chronic, ambulatory
103	McKen	4973	20	57.0	4/15	0.0	1.43	9.3	4.80	11.0	27.1	7.1	1.2	Acute attack, bed
104	Sehn	3899	25	61.0	4/26	0.0	1.30	7.9	6.72	7.4	23.1	7.3	0.7	++ Wassermann
105	Jan	4238	32	59.5	3/27	0.0	1.95	12.4	10.40	6.9	24.0	7.8	1.7	Chronic, ambulatory
106	Hick	4803	47	74.5	4/12	0.0	1.49	7.4	7.25	7.6	22.9	7.8	1.2	Chronic, ambulatory
107	Jeff	1525	24	56.4	4/12	0.0	1.26	8.4	4.10	8.7	30.8	7.9	1.0	Chronic, ambulatory
Averages						0.023	1.41	8.1	8.00	5.27	27.6	5.27	1.4	

\* Plasma creatin 1 3

† Plasma creatin 3 0

‡ Plasma creatin 3 3

§ Plasma creatin 3 1

nitrogen lost The quantity of creatin eliminated during starvation, then, is independent of the amount of tissue destroyed, and this creatin does not come from preformed creatin split off in the process of destruction There still remains the possibility, however, that the creatin eliminated during starvation may be synthesized from the end-product of the destruction of muscle protein In this case, the quantity synthesized, and hence the quantity eliminated, would not necessarily be directly proportional to the amount of tissue destroyed (total nitrogen) even though the utilization of creatin were completely (?) inhibited (phlorizin)

It has recently been suggested by Hunter and Campbell<sup>20</sup> that there may be a threshold for the elimination of creatin, and that certain cases of creatinuria may be accounted for on this basis They have published results of the simultaneous determination in the blood plasma and urine from which they conclude "that the concentration of creatin in the urine bears a direct relation to that in the plasma, and that a slight increase in the latter (as little as 0.1 mg per hundred cc) suffices to bring about a copious secretion" These observers suggest the interesting possibility of the dependence of creatinuria on a specific increase in renal permeability While the theory of a threshold for creatin elimination is entirely plausible, it is difficult to see how reliable conclusions with respect to such small amounts of creatin can be drawn with the use of any of the current methods for the determination of creatin in plasma

The relationship of creatinuria to excessive protein feeding has been repeatedly demonstrated during the last five years Amberg and Morrill,<sup>21</sup> Rose,<sup>22</sup> and Folin and Denis<sup>23</sup> have shown that creatinuria is a constant finding in children up to puberty Folin and Denis,<sup>24</sup> and Denis and Kramer<sup>25</sup> have presented highly important experimental data showing that the "creatin found in the urine of children is directly dependent on the intake of protein (creatin-free), being high when large quantities of protein are ingested, decreasing and in some cases disappearing entirely when the child is fed a diet of an extremely low protein content" Denis and Kramer point out further, that "the low saturation point of immature muscle suggested by the small creatin content of the muscles of children, and the relatively low level of protein consumption at which creatin is excreted, may account in part for the creatinuria" The relationship of high protein feeding to

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20 Hunter and Campbell J Biol Chem 33 188, 1918

21 Amberg and Morrill Ibid 3 311, 1907

22 Rose, W C Ibid 10 265, 1911

23 Folin and Denis J Biol Chem 11 253, 1912

24 Folin and Denis Ibid, Loc Cit

25 Denis and Kramer J Biol Chem 30 189, 1917

creatinuria has been further studied by McCollum and Steenbock<sup>26</sup> working with pigs and by Denis and Minot<sup>27</sup> working with adult women and persons suffering with hyperthyroidism

On the other hand, Rose, Dimmitt and Bartlett<sup>28</sup> were unable to produce creatinuria on the amount of protein that they gave their subjects but, as pointed out later by Denis and Minot,<sup>29</sup> it is necessary to give much more protein (as much as 33 gm of nitrogen per twenty-four hours) than Rose, Dimmitt and Bartlett gave, and it is also desirable to precede the period of excessive protein intake by a period of high protein feeding

That the creatinuria of excessive protein intake might be due to an acidosis caused by the highly acid character of the protein diets, has been amply precluded by recent work of Denis and Minot<sup>30</sup> who have shown that the creatinuria persists unaltered, even though the urine is kept alkaline (administration of sodium bicarbonate) and by the work of Steenbock and Gross<sup>31</sup> who have shown that sufficiently high protein diets will always produce creatinuria in pigs, even in the presence of alkalosis

Although Cathcart and Taylor,<sup>32</sup> from experiments on partially phlorizinized dogs, were led to conclude that the processes leading to acidosis and creatin elimination are distinct, nevertheless, Underhill<sup>33</sup> has shown that creatinuria would make its appearance in rabbits fed on diets rich in acid salts or on basic diets, to which hydrochloric acid had been added and would disappear on feeding basic diets. Moreover, Underhill and Bauman,<sup>34</sup> working with animals to which they administered hydrazin sulphate, were able to demonstrate creatinuria both in the presence of acidosis and a normal carbohydrate intake and in the absence of acidosis in the presence of hypoglycemia

Unfortunately, most of the observations on creatinuria and acidosis have been confused by the presence of carbohydrate starvation, so that it cannot be regarded as settled that acidosis alone is capable of producing creatin elimination<sup>35</sup>

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26 McCollum and Steenbock *Ibid* **13** 209, 1912

27 Denis and Minot *Ibid* **21** 561, 1917

28 Rose, Dimmitt and Bartlett *Ibid* **24** 601, 1918

29 Denis and Minot *Loc Cit*

30 Denis and Minot **37** 245, 1919

31 Steenbock and Gross *J Biol Chem* **36** 265, 1918

32 Cathcart and Taylor *J Physiol* **41** 276, 1910

33 Underhill, F P *J Biol Chem* **27** 127, 1916

34 Underhill and Bauman *Ibid* **27** 151, 1916

35 Many of the reported findings of creatin in urines (and bloods) containing aceto-acetic acid are doubtful inasmuch as the aceto-acetic acid causes too low results for creatinin. On boiling, the acid is destroyed and a higher value is obtained which may be taken for creatin



In 1907, Cathcart<sup>36</sup> first suggested a relationship between faulty carbohydrate metabolism and the elimination of creatin. The relationship has been further studied by Underhill and Kleiner,<sup>37</sup> who showed that hydrazin sulphate caused a marked hypoglycemia and creatinuria by Mendel and Rose,<sup>38</sup> who showed that carbohydrate food administered to starving rabbits showing creatinuria would immediately cause the cessation of the creatin elimination, whereas protein would not, and by Rose,<sup>39</sup> Wolf<sup>40</sup> and S. R. Benedict and Osterberg.<sup>41</sup> The last named investigators, whose work is quoted above, carried out an extensive series of experiments on phlorizinized dogs, from which they concluded that "the power of the organism to metabolize the creatin which it forms is directly related to certain other processes, chief among which appears to be the utilization of carbohydrate."

The bulk of evidence in regard to the origin and fate of creatin would seem to indicate that that substance is not derived from pre-formed creatin of muscle as once believed, but rather that it is constantly being formed in the body, possibly synthesized from the amino-acids produced in the intermediary metabolism of proteins, whether these come from the food or the body (starvation), and is, under normal circumstances, being retained in the body or utilized for constructive purposes. It may be eliminated in the urine when produced in excess of the absorption capacity of muscles (high protein feeding in childhood), possibly in uncomplicated acidosis, and when its retention or utilization is inhibited by factors that interfere with the utilization of carbohydrate (fasting and the more complete forms of carbohydrate starvation [phlorizin] and in diabetes mellitus<sup>43</sup>). There is no

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36 Cathcart J. *Physiol* **25** 500, 1907

37 Underhill and Kleiner. Quoted by Underhill and Bauman, *J Biol Chem* **27** 151, 1916

38 Mendel and Rose. *Ibid* **10** 213, 1911

39 Rose, W. C. *Ibid* **10** 265, 1911

40 Wolf. *Ibid* **10** 473, 1912

41 Benedict, S. R., and Osterberg, E. *J Biol Chem*, Loc Cit

42 Wolf (*J Biol Chem* **10** 473, 1912) has shown that feeding of protein to starving dogs causes a disappearance of the creatinuria and, more recently, Rose, Dimmitt and Cheatham (*J Biol Chem* **26** 339, 1916) have shown that by feeding protein to starving men the creatin output can be reduced to nil. These findings in no way vitiate the hypothesis that carbohydrate food is necessary for the retention or utilization of creatin inasmuch as Lusk has shown that a considerable part of the protein in starving dogs and men is converted into carbohydrate (glucose).

43 Numerous attempts have been made to determine the origin of creatin by feeding a possible precursor, as for example, arginin (Inouye), guanidin acetic acid (Jaffe), cholin and lecithin (Koch). Owing to the fact that large amounts of creatin can be ingested without the production of creatinuria, it would seem that any attempt to feed a precursor of creatin and recover creatin in the urine should be doomed to failure, inasmuch as the body would take care of any creatin formed just as it does the ingested creatin.

undisputed evidence to show that any important part of the creatin formed in the body is converted into creatinin

In 1918, Janney and Isaacson<sup>44</sup> demonstrated a marked glucose intolerance in cases of hyperthyroidism, and a definite and more or less characteristic glucose intolerance has been demonstrated by Pemberton and Foster<sup>45</sup> in cases of arthritis. Inasmuch as creatinuria has been demonstrated in hyperthyroidism (after high protein feeding) and in other conditions where there is a disturbance in the body's capacity to utilize carbohydrate, it was deemed worth while to investigate a series of arthritics with a view of determining the presence of abnormalities in the metabolism of creatin as revealed by blood and urine analysis. It was planned to study cases first on an average diet and then on diets containing no carbohydrates and an excess of protein with and without creatin added. Owing to the closing of the hospital, it was not possible to complete these investigations as originally planned, but the data collected seemed to be of sufficient technical and general medical interest to warrant publication.

#### METHODS

(a) *Description*—The determinations of creatin and creatinin in blood and plasma were made by the methods of Folin,<sup>46</sup> the picric acid solution being precipitated and made alkaline by the use of the potassium hydroxid-potassium chlorid mixture recommended by Folin and Doisy.<sup>47</sup> The determination of creatin in urine was made by the Folin method.<sup>48</sup> The conversion of urinary creatin into creatinin was effected by the autoclave procedure of Meyers and Benedict.<sup>49</sup> Several determinations of picric acid on blood were made by the Denis method and these also are reported.<sup>50</sup> For the determinations of total nonprotein nitrogen in both blood and urine, the direct nesslerization method of Folin and Denis was used.<sup>51</sup> Considerable difficulty was experienced

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44 Janney and Isaacson. Arch. Int. Med. **22** 160 (Aug.) 1918.

45 Pemberton and Foster. Part III, Studies on Arthritis in the Army, Arch. Int. Med. **25** 243 (March) 1920.

46 Folin. J. Biol. Chem. **17** 475, 1914.

47 Folin. Ibid. **27** 349, 1916.

48 Folin. Ibid. **17** 164, 1914.

49 Benedict, S. R. Ibid. **18** 191, 1914. The creatinin used in preparing the standard solutions was presented to the laboratory through the courtesy of Prof. S. R. Benedict. The standard solutions were kept in dark glass bottles and no standard over six weeks old was used. (See Hunter and Campbell. J. Biol. Chem. **28** 335, 1916.)

50 Denis. J. Biol. Chem. **35** 513, 1918.

51 Folin and Denis. Ibid. **26** 491, 1916. It was found that the metaphosphoric acid with which we coagulated the proteins contained a small amount of nitrogen, sufficient to elevate the total nonprotein nitrogen by from 18 to 26 mg. per hundred cc. of blood. The proper deduction was made in each case. Since the analyses were made, Folin has pointed out (personal communication, May 19, 1919) that this nitrogen can be removed by fusing 100 gm. of the metaphosphoric acid with from 1 to 2 gm. of potassium nitrate.

TABLE 2—DETERMINATION OF CREATIN AND CREATININ IN BLOOD AND URINE OF ARTHRITIS PATIENTS

Name Case Registration No Operation	Date	Urine Gm per 24 Hours					Blood Mg per 100 C c			Clinical Data
		Total Nitrogen	Creatinin	Creatinin Nitro- gen, Weight	Creatin	Creatinin Nitro- gen Total Nitrogen	Creatinin Whole Blood	Creatin Whole Blood		
Jaf Case 7 Reg No 1525 Tonsillectomy 1913	3/27/19	6.73	1.33	9.15	0.0	7.29	3.0	3.8	30.0	Subacute, ambulatory pain in knees and heel Considerable improve- ment since last test
	4/12/19	4.10	1.26	8.37	0.0	8.73	1.0	7.9	30.8	
Hin Case 11 Reg No 2503 Tonsillectomy 4/3/19	3/31/19	7.58	1.56	10.40	0.0	7.68	1.1	5.9	28.6	Subacute, ambulatory, chronic tonsillitis Some improvement
	4/14/19	5.80	1.42	9.23	0.0	8.97	1.4	5.5	31.9	
Jan Case 48 Reg No 4238	3/27/19	10.40	1.95	12.40	0.0	6.91	6.0	7.82	24.0	Chronic, ambulatory, walks with cane Slight improvement since last week Marked improvement, can walk without cane
	4/14/19	6.46	1.86	11.60	0.0	10.80	5.2	6.0	26.2	
	5/ 5/19	8.15	1.37	8.68	0.0	6.23	1.1	3.9	30.8	
Cha Case 47 Reg No 4049 Tonsillectomy 3/12/19	4/14/19	10.45	1.76	9.39	0.16	6.22	1.5	7.0	34.5	Chronic, ambulatory, with crutches Acute attack, in bed, no fever Symptoms still present but much improved
	4/22/19	6.90	1.06	5.84	0.40	5.64	1.2	7.1	27.1	
	5/ 8/19	10.80	0.89	4.76	0.0	3.03	0.8	5.2	24.9	
Hie Case 76 Reg No 4803	4/12/19	7.25	1.49	1.38	0.0	7.58	1.2	7.8	22.9	Subacute, ambulatory Symptoms still persist but definitely improved
	5/14/19	6.47	1.09	5.40	0.0	6.25	1.0	4.5	25.5	
McK Case 62 Reg No 4973	4/15/19	4.80	1.43	9.34	0.0	11.00	1.3	7.30	30.9	Chronic, ambulatory Acute attack, in bed, CO <sub>2</sub> 40.4 vol per cent acetylsalicylic acid t i d during 3 days of test, febrile
	4/30/19	8.18	1.82	11.95	0.0	8.25	1.2	5.03	28.5	
Lyn Case 52 Reg No 4836 Tonsillectomy 4/7/19	4/17/19	4.60	1.03	6.25	0.0	8.38	1.4	6.00	30.9	Chronic, ambulatory Marked improvement
	5/13/19	6.16	1.31	7.90	0.0	7.90	0.8	4.4	29.0	
Mil Case 61 Reg No 5313 Tonsillectomy 5/1/19	4/24/19	9.16	1.39	9.73	0.0	5.70	0.77	6.6	24.1	Acute attack, in bed, Temp 100 first day of diet, acetylsalicylic acid t i d for 3 days of diet No symptoms
	5/13/19	10.82	1.39	8.86	0.0	4.68	0.9	5.4	30.7	
Her Case 60 Reg No 4804	4/20/19	6.07	1.70	9.30	0.0	10.30	1.4	5.4	22.1	Acute attack, in bed
Io Case 14 Reg No 3759	4/ 7/19	6.26	1.52	7.75	0.097	8.94	0.7	7.0	30.0	Chronic in bed No improvement
	5/ 9/19	7.23	1.46	7.70	0.0	7.51	1.1	6.8	29.1	

in securing pure picric acid. Samples from four different manufacturers were tested, and all of them, until purified, proved unsatisfactory on account of the marked darkening which took place on boiling, autoclaving, or on neutralizing with alkali. The several samples were purified twice by the method suggested by Folin and Doisy<sup>52</sup>. Only those samples were used for the preparation of standards or for analysis whose color became less than half again as intense on neutralizing with alkali, which showed no change of color on autoclaving and to which creatin could be added, the solution autoclaved, and the creatin recovered quantitatively (colorimetrically) as creatinin.

TABLE 3—CREATIN AND CREATININ VALUES FOR WHOLE BLOOD AND PLASMA (FOLIN METHOD) \*

Registration Number	Date	Creatin		Creatinin	
		Whole Blood	Plasma	Whole Blood	Plasma
3689	5/ 1	29	15	09	08
3550	4/28	36	13	18	13
4238	5/ 3	39	22	10	14
1099	5/ 3	40	13	11	09
4257	5/11	41	19	09	08
6	5/12	46	13	06	08
4	5/10	46	15	10	10
5054	4/26	47	30	15	14
5443	5/11	48	18	10	07
4997	5/ 5	49	18	14	15
4973	4/30	50	27	12	10
4804	4/26	52	27	14	16
2503	3/31	59	25	11	10
4238	4/ 7	60	24	52	48
4836	4/17	60	22	13	11
3559	5/ 9	68	30	11	10
4049	4/14	70	33	15	16
3559	4/ 7	70	30	07	10
5313	4/24	70	17	08	08
Averages		54	22—	13	12

\* Values for creatin and creatinin are mg per hundred c.c. of whole blood or plasma

(b) *Discussion*—It appears to be fairly definitely settled that determinations on both whole blood and plasma by the Folin method and presumably also by the Denis method, represent the truth so far as creatinin is concerned. Yet it is equally true that when values for creatin in blood or plasma are published, they constitute a *casus belli*.

In concurrence with the work of Hunter and Campbell,<sup>53</sup> our results show a fairly uniform distribution of creatinin between plasma and corpuscles (whole blood) (Table 3). Moreover, our values for creatin in the plasma are lower, as were theirs, than the values for creatin in whole blood, markedly and uniformly so throughout the entire series. A striking fact about these creatin values is that the values for plasma do not parallel at all the figures for whole blood.

<sup>52</sup> Folin and Doisy. J. Biol. Chem. **27** 349, 1916

<sup>53</sup> Hunter and Campbell. Ibid. **33** 169, 1918

A number of determinations were also made by the Folin method and by the Denis method (Table 4) on the same sample of whole blood. In agreement with Denis' work,<sup>54</sup> our values for creatinin are slightly lower and those for creatin markedly lower by the Denis method than by the Folin method. However, in attempting to apply the metaphosphoric acid precipitation method to plasma, we found, in many instances, extremely small values for creatin—in some cases less than 0.5 mg per hundred c.c. This observation and the finding of

TABLE 4—COMPARATIVE ANALYSES OF WHOLE BLOOD FOR CREATIN AND CREATININ BY THE FOLIN AND BY THE DENIS METHOD

Sample	Creatin		Creatinin	
	Folin Method	Denis Method	Folin Method	Denis Method
27	6.0	2.5	1.4	1.3
28	5.2	2.3	1.3	1.3
29	4.9	2.8	1.5	1.2
30	4.5	3.4	1.2	1.0
31	7.1	3.5	1.2	1.0
32	4.8	3.0	1.2	1.2
33	6.6	3.3	0.8	1.4
34	6.1	3.8	1.7	1.9
35	4.7	1.8	1.4	1.8
36	5.4	2.5	1.4	1.4
37	3.6	2.6	1.8	1.6
38	3.4	3.2	1.6	1.8
39	3.8	1.8	1.3	0.9
40	4.2	2.5	1.5	1.4
41	5.0	2.1	1.2	0.6
42	2.9	2.9	0.9	1.0
43	4.4	3.0	0.9	0.7
44	4.2	1.8	1.4	1.2
45	3.5	2.1	1.3	1.4
46	5.7	1.8	1.0	0.9
47	4.0	1.3	1.1	1.0
48	3.9	1.5	1.0	0.9
49	4.9	2.4	1.4	1.4
50	4.0	3.6	0.7	1.5
51	5.2	2.5	0.8	1.0
52	4.4	2.3	0.9	1.1
5	4.6	2.0	1.0	1.0
4	3.7	2.4	1.1	1.2
53	4.8	2.3	1.0	1.0
54	4.1	3.2	0.9	1.3
6	4.6	2.5	0.6	0.6
7	4.0	2.1	0.8	0.7
Averages	4.8	2.7	1.6	1.3

Greenwald<sup>55</sup> that certain protein precipitants, notably methyl alcohol, occlude creatin and certain amino-acids, led us to start an investigation to determine, if possible, to what extent the various protein precipitants (picric acid, trichloroacetic acid, metaphosphoric acid, methyl alcohol, tungstic acid<sup>56</sup>) occlude creatin. As yet, we have not made a sufficiently large number of determinations to draw any definite conclusions, but publish here (Table 5) a few of our results obtained from precipitating the proteins of whole blood and plasma with picric acid and metaphos-

<sup>54</sup> Denis. *Ibid* **25** 513, 1918

<sup>55</sup> Greenwald. *Ibid* **21** 61, 1915

<sup>56</sup> The use of this last was suggested by Folin (personal communication)

phoric acid The method employed was briefly as follows About 30 c c of blood from an arm vein were aspirated into a small Erlenmeyer flask containing about 0.1 gm of potassium oxalate<sup>57</sup> Ten c c of this mixture were taken for the determination of creatin and creatinin in whole blood The balance was centrifuged (at 2,000 revolutions per minute for 10 minutes) and the plasma pipetted off Definite volumes of plasma and corpuscles were then taken for analysis The corpuscles were laked by making up to a definite volume with distilled water In a given sample the same precipitant was used for coagulating the

TABLE 5—COMPARATIVE VALUES OF YIELD (CREATIN AND CREATININ) FROM SUPERNATANT LIQUID AND COAGULATED MASS PLASMA (PL) AND WHOLE BLOOD (W B), MG PER HUNDRED C C

Method	Sample	Whole Blood			Plasma		
		Super natant Liquid	Super- natant Liquid plus Coag- ulum	Percentage of Total from Super- natant	Super natant Liquid	Super natant Liquid plus Coag- ulum	Percentage of Total from Super natant
Denis	10	6.8	7.8	82	1.1	2.5	44
	11	3.8	4.9	78	2.9	4.2	69
	6	4.2	4.5	94	2.5	2.8	89
	7	3.9	4.2	93	2.5	3.4	74
	12	4.7	5.5	86	2.2	4.0	55
	13	2.4	3.1	77	1.2	2.5	48
	14	6.6	8.5	78	1.6	3.0	53
	15	3.8	4.3	86			
	16	3.6	4.2	86			
	17	4.1	4.8	85			
	18	4.5	5.1	88			
	19	4.1	5.2	79			
Folin	20	4.6	5.1	90	2.0	3.0	67—
	21	7.0	8.4	83	3.4	4.0	85
	4	5.9	7.5	79	4.9	5.1	96
	5	5.2	6.5	80	3.8	4.4	86
	22	5.9	8.3	71	4.0	5.1	80—
	23	6.6	7.4	89	3.6	4.2	81—
	24	6.2	7.4	84			
	25	6.2	8.1	77			
	26	6.8	9.0	76			

Average percentage yields from supernatant fluid

Denis Method Whole blood, 84.5 per cent, plasma, 61.7 per cent

Folin Method Whole blood, 81.0 per cent, plasma, 82.5 per cent

proteins of whole blood plasma and corpuscles After coagulating the proteins in each, the suspension was centrifuged (2,000 revolutions per minute for 10 minutes) and the supernatant liquids were analyzed for creatin and creatinin The coagulated masses from whole blood, plasma and corpuscles were separately washed thoroughly with five 50 c c portions of distilled water (further washing did not increase the yield), the washings added together and concentrated in acid (normal) solution and then analyzed for creatin plus creatinin

The results presented in Table 5 suggest that a considerable amount, roughly 20 per cent, of the creatin of whole blood (we have figures

<sup>57</sup> Folin J Biol Chem 17 475, 1914

to show that the creatinin is but little, if at all occluded) is occluded in the coagulated proteins, and that in plasma, precipitated with metaphosphoric acid, a relatively larger amount of creatin is occluded. Moreover, in a few determinations which we have made on the corpuscles (metaphosphoric acid) we have found from four to five times as much creatinin plus creatin in the coagulum as in the supernatant liquid. These results suggest that the corpuscles may contain some chromogenic substance other than creatin which, on autoclaving, gives a color with picric acid. Investigations have been started involving the addition of known quantities of creatin and creatinin to whole blood, corpuscles and plasma in the hope of throwing further light on this problem.<sup>58</sup>

The determinations of creatinin and creatin on whole blood and urine shown in Tables 1 and 2 were all made with picric acid precipitation. While determinations of creatin in whole blood or plasma by any of the current methods admittedly may not represent actual quantities of creatin present, nevertheless, such determinations are of value in a statistical study as showing an empirical departure from the normal. At least this is all that can be said of them until more accurate methods are introduced.<sup>59</sup>

### SUBJECTS

The nine normal controls were volunteers from the medical corps detachment of the hospital. The cases reported were all of them hospital patients suffering from arthritis in various stages of the disease, from acute attack to well advanced convalescence. In every case (patient or normal control), the individual was put on a creatin- and creatinin-free diet for a period of three days, and on the fourth day, before breakfast the sample of blood was taken. The urine used for analysis was that obtained during the last twenty-four hours. The diet averaged 50 gm of protein, 65 gm of fat and 300 gm of carbohydrate, yielding about 2,000 calories. Only two of the cases were febrile during the period of observation (these so noted).

### OBSERVATIONS ON THE RESULTS

1 In Table 1 are recorded the results of the analyses of the blood and urine of nine normal controls and fifty cases of arthritis in various stages of the disease. These cases are arranged according to ascending

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58 The studies forming the basis of Tables 4 and 5 were contributed by Lieutenant Buckman alone.

59 This work was completed before the system of blood analysis by Folin and Wu was published. Folin and Wu. *J Biol Chem* 38 81, 1919.

values for "creatin" in whole blood Broadly speaking, about half of these show values for blood "creatin" above the highest normal value

2 Many of the high values for creatin in the blood seem to fall in that group of cases characterized by very acute symptoms or by a very chronic course without much change from day to day

3 Despite the definite glucose intolerance shown by a majority of the cases (see Part III) only three of the cases show creatinuria on the diet given This creatinuria cannot be attributed to dietary factors

4 In three of the four instances in which creatinuria occurred, there was a distinct elevation of the creatin of the plasma, but in the fourth instance it was only 1.3 mg per hundred c c

5 Two cases, one on two observations, showed very high values for creatinin in whole blood (4.6, 5.2 and 6.0 mg per hundred c c) with normal values for total nonprotein nitrogen in the blood It is remarkable that in one case in which a third creatinin determination was done, the value fell to normal simultaneously with marked clinical improvement of the patient

6 Fully one-fourth of the cases show an abnormally low creatinin elimination, not attributable to diet (starvation) But, as Shaffer<sup>60</sup> pointed out, this is seen in a large variety of pathologic conditions and is not characteristic of any particular disease group

7 About one-third of the cases did not reach the level of nitrogen elimination indicated by the diet in the three day period allowed

8 Only two cases out of the entire series show an abnormal elevation of the total nonprotein nitrogen of the blood

9 In Table 2 are presented ten cases In nine of these, at least two determinations at different stages of the disease were made Seven of these show a fall in the creatin content of the blood simultaneously with clinical improvement Two showed the opposite One shows no change in the creatin content of the blood, and no change clinically

#### SUMMARY

1 Determinations of the creatin, creatinin, and nonprotein nitrogen of the blood and urine of forty cases of arthritis and nine normal controls are presented About one-half of the cases of arthritis show an abnormally high value for blood creatin

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<sup>60</sup> The average normal values for creatinin in whole blood are generally given as from 1 to 2 mg per hundred c c There is a great discrepancy regarding normal average values for creatin Hawk (Loc Cit) gives 3 mg per hundred c c Hunter and Campbell give 5.52 (uncorrected) mg per hundred c c Our own figures are somewhat lower, 4.3 mg per hundred c c



2 A certain number of patients show a decline in blood creatin simultaneous with clinical improvement

3 Only three of the cases show creatinuria

4 Only two cases show an abnormal elevation of nonprotein nitrogen of the blood

5 Figures are presented which suggest that a considerable amount of creatin is occluded in the precipitation of the proteins of whole blood and plasma

# STUDIES ON ARTHRITIS IN THE ARMY BASED ON FOUR HUNDRED CASES

V ROENTGEN-RAY EVIDENCES, CLINICAL CONSIDERATIONS, TREATMENT,  
SUMMARY, CONCLUSIONS AND CLINICAL ABSTRACTS  
OF CASES STUDIED

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## ROENTGEN-RAY EVIDENCES

Roentgen-ray studies were made in all cases of the 400 in which there was any suspicion that there might be additional evidence discoverable by these means. One hundred and seventy-nine series of plates were made, ranging from one to twenty plates in any given series, and the percentage of positive findings justified omitting recourse to the roentgen ray in the absence of such suspicion.

The total number of cases of arthritis studied was 400. One hundred and forty-seven cases, or 37 per cent, were studied with the roentgen ray. Forty-six cases, or 31 per cent of the 147, gave positive roentgen-ray findings. The forty-six cases giving positive roentgen-ray findings constituted  $11\frac{1}{2}$  per cent of the whole series of 400 cases. In other words, making allowances for cases which may have been overlooked, it is clear that a relatively small number of the entire series, say less than 15 per cent, showed evidences of bony change when examined by the roentgen ray.

This is of some interest in the light of our being able to date the onset of arthritic manifestations in most cases from a certain given period, and often abruptly from a fixed date. It is not at this time possible to give the approximate duration of disease necessary in these cases for the production of bony change giving roentgen-ray evidence, but it is clear in the group studied that arthritis, and its accompanying phenomena, may exist for many months, producing gross superficial changes without resulting in evidence that the roentgen ray can detect, except in the increased shadows of the soft parts.

It is common experience in civil life that the bulk of patients presenting chronic arthritis show definite roentgen-ray evidences by the time they apply for treatment. It early became apparent, however, in

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\*I desire to express obligation for the helpful cooperation of Lieut Milton C Glover M C, chief of the roentgen-ray laboratory, and Lieut William A Newell M C.

this series that for purposes of determining the severity of symptoms, or presenting evidence before disability boards, negative roentgen-ray findings could not be depended on as proof that disability did not exist. It was in some cases a matter of the greatest difficulty to decide whether the patient did or did not have pain or limitation of function. Of completing our analysis of 420 cases, we came to regard roentgen-ray evidences as implying in general a marked degree of chronicity. Practically all of the advanced changes met with in civil life were reflected in this series, and certain soldiers showed the most pronounced pathologic evidences from the roentgen-ray standpoint.

The cases in which, perhaps, roentgen-ray evidence was most frequently desired but was apt to be lacking were those in which disabilities were referred to the back, including spondylitis, paravertebral myositis, sacroiliac disease, etc., in which differential diagnosis was difficult. The evidence was frequently deficient in these cases, not only because good roentgenograms of the spine are often obtained with difficulty, but because much time is required for an arthritis of the several articulating vertebral structures to exhibit pathologic processes detectable by the roentgen ray.

In making provision for the treatment of a group such as has been considered here, elaborate roentgen-ray equipment and a well experienced personnel would be essential.

#### CLINICAL CONSIDERATIONS

A clinical survey of the topic herewith presented develops a number of points of interest. The cases occurring under military conditions differ from those met with in civil life in respect, chiefly, of the age, the immediately exciting factors and the greater tendency to improve. It was found that nearly all types encountered in civil life were represented, although the incidence of some varieties was different. In general, the age of the individual and the relatively limited chronicity of the disease precluded the occurrence of gross lesions of the degree and frequency met in the later decades of life. It was in some part because of this limited organic change that gratifying end-results could be achieved, making this group particularly worthy of therapeutic effort. Although chronic arthritis in the young is not a rare disease, and some of the most refractory cases occur at this age, nevertheless, its frequency is vastly increased by war conditions, and this situation presented unusual opportunity for observing the problem in large numbers of men from a new angle.

Because of the lesser frequency of structural bony change, and the gross evidence thereof, it was sometimes difficult to reach decisions as to the existence or degree of disability. As mentioned under the section on roentgen-ray findings, cases involving the spine and sacro-

iliac joints presented the greatest difficulty in diagnosis. There were many instances of lowered function in bending forward, accompanied often by some pain in the lower spine, in the paravertebral regions, or in the sacroiliac joints, although outstanding and severe disabilities of this nature were not of great frequency<sup>1</sup>

The minor neuroses, secondary to illness and war conditions in general, often complicated the picture. A certain number of cases showed acute tenderness to pressure at and below the costal borders posteriorly, suggesting, but not simulating, lumbago.

A small number of cases called to mind the picture presented by certain supposedly neurotic conditions, unaccompanied by organic change, in which the individual bends forward as though the subject of advanced vertebral disease (Case 48, Jansen). Under the heading "*camptocormie, spondylose antalgique*" and other titles, the French have directed considerable attention to this subject, and the diagnosis between it and *spondylitis deformans* is acknowledgedly difficult<sup>2</sup>. For the reasons mentioned under the preceding paragraphs and under "*Roentgen-ray Evidences*," the conclusion was reached that in the presence of disabilities referred to the back as a whole, it was unsafe to deduce without prolonged, exhaustive observation that organic disease was not present.

The exciting factors other than exposure, need a little comment. It is somewhat surprising that dysentery should occupy the second place. The evidence respecting this and the next most frequent exciting factor, "flu," was obtained from the service records of the men, and from a very close questioning as to their whereabouts and condition at the time of the onset of the arthritis, and is hardly open to serious error. The arthritic attack came on at all stages of the apparently causative disease, but one interesting point was developed in respect of the occasional onset of rheumatic disability nearly or quite coincident with convalescence, when the conditions of life were not adequate to explain it. This point is deserving of further scrutiny, and was illustrated in about thirteen clear instances of which the following cases are typical. Only the last 150 cases, or so, were closely analyzed in this regard, but other cases seen earlier will be suggested by reference to the "*Clinical Abstract of Cases Studied*."

<sup>1</sup> A brief but comprehensive survey of back disabilities in the army is given by Sherwood and Jones (*J A M A* **72** 1599 [May 31] 1919). They call attention to the frequency of sacroiliac conditions, the infrequency of malingerers, and the great difficulty in reaching a correct diagnosis. This is in agreement with our experience.

<sup>2</sup> Hall, G. W. *Camptocormia (Bent Back)*, *J A M A* **72** 547 (Feb 22) 1919. Saliba, John. *Antalgic Spinal Distortion* *J A M A* **72** 549 (Feb 22) 1919.

## CASES OF ARTHRITIS OCCURRING DURING CONVALESCENCE

CASE 1—Miss T, aged 24 years, army nurse corps, contracted influenza at Camp Grant Oct 11, 1918. She was sick for four days and after two days of convalescence, up and about, returned to duty. In about a week she developed pleurisy and went to bed for about four weeks. At this time the effusion, which was serous, had apparently been absorbed and she was allowed to get up. After three days of convalescence, up and around the ward, she suddenly developed multiple severe arthritis which still incapacitated her, with some active symptoms as well as sequelae, eight months later. Dental foci of infection were removed at Camp Grant by extraction of teeth. Another dental focus was removed May 2, 1919, at U S Army General Hospital No 9, Lakewood, N J. The tonsils were reported negative. The genito-urinary tract was not examined.

CASE 2—Private Reap, aged 25 years, did full infantry duty in France until Sept 27, 1918, when he was knocked down by a high explosive shell but was otherwise uninjured. Six hours later he received a perforating wound of the right leg from a machine gun bullet. He reached a base hospital four or five days later and was in bed for three weeks. A week or two later, while going around on crutches, arthritis developed, first in the knees then in the hips and shoulders. He made a full recovery in the presence of a dental focus, although for some months he was rather depressed psychically.

CASE 3—Sergt Herron (Case 60), aged 24 years, while doing full duty in the field artillery was operated on for a ruptured gangrenous appendix in February, 1917, followed by drainage for seventeen days. About April, 1917, after recovery, he was returned to light duty. About May 1, 1917, he first noticed aching in his hips. He had never had any previous attacks of rheumatism and could not ascribe the onset to exposure to cold or wet. In a few days, hands, fingers and knees became involved, but after running a protracted course, he was returned to full duty. In June, 1918, he contracted influenza and spent ten days in the hospital. He was then returned to full duty on outdoor work, but was not exposed to cold or wet. After two weeks he suddenly developed an arthritis in the right hip and knee. The disease spread to many other joints and in June, 1919, he was still invalided, suffering from sharp exacerbations. He had apparently had no foci of infection in the teeth, tonsils or the genito-urinary tract at the time of the onset, and no demonstrable surgical focus was discovered even after repeated examinations at U S Army General Hospital No 9.

CASE 4—Private Moore, aged 25 years, gave a history of having had rheumatism in the lower limbs for four weeks in 1915. After his recovery, two teeth were extracted. He did full duty in a machine-gun battalion. Early in October, 1918, he was gassed, this was followed by vomiting and bloody diarrhea, lasting about two weeks. He was sent to a field hospital for five days, and was then returned to full duty. A day or two after return to full duty, his diarrhea and vomiting having both ceased for a similar period, rheumatism came on in the right ankle while marching, spreading in a few days to the knee and back. He made full recovery in the presence of a probable focus in the tonsils.

CASE 5—Lieut Jaycox, infantry, aged 54 years, had never had a previous attack of rheumatism and did work as transport officer in the Argonne sector. In the last week of July, 1918, dysentery developed. It ceased about September 1. After this attack he returned to full duty, the diarrhea remaining in abeyance without medication. Toward the end of September he suffered for three or four days with some diffuse stiffness. October 1, he was sharply incapacitated by involvement of the right shoulder, knee, ankles and lumbar spine. This officer made a considerable but slow improvement in the presence of a tonsillar focus, removal of which was contraindicated.

CASE 6—Private Tingle (Case 95), aged 27 years, had had rheumatism of the left knee at the age of 14. He did full duty overseas. In August, 1918, he suffered from dysentery which he says was epidemic in the division at that time. The dysentery lasted about two weeks and then practically ceased. After having had no medicine for his bowels for two or three days, and while doing full duty, both knees became swollen, confining him to bed. His hips and left shoulder became involved later. He occasionally had a return of the looseness of the intestines in the hospital, but never more than three or four times a day. He was still invalided in May, 1919, during which month a tonsillar focus was removed at U. S. Army General Hospital No. 9.

It is, of course, entirely possible, theoretically, that when exposure acted as the exciting agent in producing arthritis, it did so through the intermediation of a focus of infection by lowering the general resistance to such infection or by favoring the growth or extension of such a focus until it assumed systemic importance. It is unnecessary to assume such intermediation, however, in the instances caused by dysentery and influenza, although it may exist. The large independence as regards focal infection shown by these men during their convalescence, the abrupt onset following exposure in many cases, the absence of demonstrable foci in many, the failure of removal of foci to affect some, and other considerations, make it unsafe to assume that all cases are caused by this intermediation. It is probable that the question cannot be settled as yet, and that we must admit the possibility that exposure per se is capable of inducing "rheumatic" disability.

Very few of the 400 patients studied presented any important intercurrent conditions. Cardiac involvement was negligible, except in a few who gave clear histories of acute inflammatory rheumatism. This bears out the experience of civil life in which there is apparently complete independence of chronic arthritis and cardiac affections, although acute inflammatory rheumatism, complicated, by valvular disease, may, of course, be subsequently followed by chronic arthritis. It is possible that the emphasis placed on cardiac examination in the draft largely prevented the occurrence of such types.

Although many of the cases of this series had a febrile onset, probably in only a small number was this representative of what is properly known as acute inflammatory rheumatism. A small number of cases under our observation ran an acute inflammatory course, with effusion, swelling, pain and loss of function. These patients made a rapid convalescence and sometime later, developed another attack but could not properly be classed as cases of acute inflammatory rheumatism. On several counts it seems clear that in addition to the low grade fever sometimes encountered in chronic arthritis, this disease may manifest itself in sharper outbreaks with higher fever, shorter course and no residual arthritic or cardiac pathology. It is difficult or, perhaps, impossible at present to draw a line sharply between chronic arthritis

which includes these occasional manifestations and acute inflammatory rheumatism itself, and several cases of this series appeared to merge from one condition into another.

Acute inflammatory rheumatism, and the exacerbations of chronic arthritis, or even chronic arthritis itself, seem, therefore, to differ in degree rather than in kind, except that circulating bacteria may cause valvulitis, emboli and sepsis. True sustained inflammatory rheumatism with valvulitis is probably due to bacterial infection only. The acute exacerbations of chronic arthritis may apparently occur in the absence of bacterial infection and may follow other causative agents. In both conditions, however, the arthritic phenomena probably result from some common intermediary step, such, for example, as that productive of a lowered carbohydrate tolerance, secondary to focal infection or other agencies.

The present series afforded interesting data as to the unusual manifestations which the "rheumatoid" state may sometimes induce. Case 22 (Oberg) described in detail under "Dietary Considerations" and under "observations on the blood sugar," was a case in point. From the clinical standpoint, there is apparently no room for doubt that the pleuritic manifestation in the left chest occurred as an exacerbation during improvement and was referable to the underlying cause of the arthritis. Following, as it did, closely on effusion into a knee joint and being accompanied by fever of only trifling degree, and by slight signs of effusion in the chest, it was at the time regarded as being rheumatic rather than infectious or bacterial in the usual sense. The next manifestation corroborated this view. A few days later, the patient developed all the clinical signs of a mild phlebitis with very slight fever, great edema of the leg, tenderness, and a mass in the upper femoral region. This, in turn, subsided.

Another case in point was that of a man (Folden, Case 63), aged 24 years, a railroad section hand in civil life, who for ten years past had had arthritic pains, worse in bad weather, chiefly in the right leg. He had suffered intermittent disability since induction, but improved sufficiently to go "over the top" once. In the course of shifting and progressive disability in his left leg and elsewhere, and about four weeks after removal of his tonsils, which constituted the only focus he developed apparent obstruction to the circulation of that leg, characterized by swelling, cyanosis, tenderness and enlargement of the inguinal lymphatics with tenderness over the popliteal and femoral vessels. This condition suggested phlebitis because of the great enlargement of the calf and cyanotic appearance of the whole limb, and was quite atypical of rheumatoid manifestations at large. It was apparently truly rheumatic, however, and was associated with pains at the costal border posteriorly, nearly complete loss of function of the

left arm from arthritis and myositis, and fever as high as 101 F. It is not inconceivable that we may come to regard certain inflammations of the serous membranes, such as the pleura, unaccompanied by any frankly rheumatic phenomena, as fundamentally referable to the same pathology which more frequently causes inflammation of the synovial membranes of joints and the other evidences of arthritis.

Studies of the morphology of the blood revealed little of interest. Considerable attention was directed by First Lieut. J. W. Sherril, director of the general laboratory at U. S. Army General Hospital No. 9, to the examination of blood smears, but no noteworthy departures were detected as to the types of cells encountered, platelets, or other elements of the blood morphology. The only point deserving of mention is the rather large number of differential blood counts showing a relatively low percentage of polymorphonuclears with a corresponding increase of the mononuclears. It could not be determined that this bore any relation to the severity or stage of the disease. The polymorphonuclears were 55 per cent or less in 21 per cent of the cases studied. They were 50 per cent or less in 8 per cent of the cases studied.<sup>3</sup> A normal or higher percentage of polymorphonuclears was a frequent concomitant of the most severe and refractory types of cases.

Twenty-eight cases, or 7 per cent of the 400 cases analyzed, showed a leukocytosis above 11,000 and under 13,000. Twenty-eight cases, or 7 per cent of the 400 cases analyzed, showed a leukocytosis above 13,000. Fifty-six cases, therefore, or 14 per cent of the 400 cases analyzed, showed a leukocytosis of more than 11,000. These figures are based on the series as a whole, irrespective of types, chronicity or severity of the disease, but do not include changes due to intercurrent conditions.

Flatfoot sometimes added to the difficulty of both diagnosis and treatment, and is a factor that should be considered in any large provision for a group such as the present. The time and attention required for the proper care of this condition could not be afforded at the hospital, although some of these cases were secondary to the arthritis after long invalidism.

In the past, much attention has been given to the clinical classifications of the various types of arthritis. It is now becoming apparent that a new and simpler classification is needed. This is indicated in part by the rôle which foci of infection are known to play in arthritis at large. The data afforded by this series of cases as to the frequency with which varying types may follow exposure, dysentery or infectious

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<sup>3</sup> Owing to the closure of the hospital and the subsequent inaccessibility of many records these percentages are based on full differential blood counts in 178 cases.



diseases of almost any kind, and the common response of many of these different types of cases to several lines of therapy, is further evidence of the common origin of many of them. There are undoubtedly cases in which hypertrophy and overgrowth of bone form the outstanding evidence. There are other cases in which atrophy of cartilage and bone is the predominating factor. It is possible, however, in the majority of cases, sooner or later to demonstrate evidences of both processes, although there are types of arthritis which must, as yet, be left within classifications of their own, for example, osteitis deformans. It seems more rational, in the light of our present knowledge, to regard the usual types as referable fundamentally to the same pathologic factors, influenced in certain cases toward the production of one clinical picture and in other cases toward another.

#### TREATMENT

The present studies as to the nature and best treatment of arthritis in the army were undertaken with the intention of finally translating overseas, to the site where most cases develop, those methods and conditions which had been found to give the best results and reach the largest number. No attempt was made to exploit any particular kind of therapy, as it was believed that only experience along various lines with this unusual group could indicate the varieties and standards of treatment best adapted to the given conditions. This belief was borne out in a practical way.

It would seem on superficial analysis that a group of cases of chronic arthritis of the size here presented would provide experiences in the various forms of therapy applied to this disease on unusually large scales. It is true, that opportunity was afforded for carrying out any given line of treatment at some length, but as stated under "Clinical Considerations" the group here discussed presented one outstanding departure from the group of arthritics encountered in civil life, namely, in respect of the greater tendency of the soldier to improve or recover in the majority of instances, if given a fair chance. A large number of patients were recovering on admission or had recovered following nothing more fundamental than rest and external measures, notwithstanding severe and protracted invalidism. This fact, together with our own experiences, forced on us consideration of the results obtained by the expectant plan of treatment when based on such measures as baking, massage, hydrotherapy, electricity and the like. These had consequences much more encouraging than are encountered in civil life, and led us to postpone certain more radical types of treatment until they were clearly indicated. It became obvious that for the group, as a whole, the importance of the above external measures, as adjuvants, at least, would have to be recognized, although this conclusion did not

apply to the most severe cases and cases of longest duration in the same degree. By and large, this group, as a whole, constituted an unintended experiment on a large scale in the artificial induction through the hardships of warfare, of rheumatic affections in young men of an age least frequently attacked by them.

It must be clearly emphasized, however, that the kinds of treatment which received greatest emphasis were, first, those based on attempts to discover and remove foci of infection when present, and second, those based on local and external measures. Other forms of therapy figured less conspicuously. As mentioned elsewhere, every case presenting on the service was thoroughly analyzed by the ear, eye, nose and throat department, the genito-urinary department and the dental department for evidences of focal infection, irrespective of whether the patient presented active symptoms or was entirely cured of the disease for which he was invalided. This was, of course, additional to a complete routine physical examination, including blood counts, Wassermann test, etc., made on admission. The analysis for foci and the action based thereon were the premise from which all other therapy started, and anything else undertaken was additional to the principle of removing causative surgical pathologic conditions. Additional therapy was instituted either pending improvement from this source or after efforts along these lines had failed. The position was taken that it was philosophically unsound to attempt to treat these patients by other means in the presence of removable and potentially causative surgical processes. There were, of course, many instances in which the existence of a surgical lesion or its relation to the disease were in question, but wherever possible, the soldier was given the benefit of the doubt. The exceptions to this rule were made in those cases in which operative procedure was contraindicated, or where after recovery, such procedure was refused by the soldier. In practically every case in which the disease was stationary, growing worse or improving unsatisfactorily, operative removal was carried out. In the case of soldiers who had made an essentially complete recovery on admission such action was made optional.

As will be seen in the statistical analysis, the tonsils formed the most frequent site of focal infection, and it would seem, from our experience with this large group, that the emphasis placed on these tissues in their relation to arthritis is, in general, justified. Two hundred and eight patients had foci in the tonsils, which is 52 per cent of the entire series and 71 per cent of those showing foci.

Thirty-four patients, or  $8\frac{1}{2}$  per cent, recovered after the removal of foci. Thirty-one patients, or  $7\frac{3}{4}$  per cent, improved after the removal of foci, but the end-result may have been favorable in certain unimproved cases which disappeared early from observation.

The varying opinions held by even experienced observers as to the existence of disease in the tonsils, the results of culture and section of the tonsils after removal, and the results of tonsillectomy itself, have emphasized the fact already indicated by others, that it is difficult or impossible to be sure that tonsillar infection does not exist, except after thorough enucleation. Only those most experienced in weighing this point are likely to advance a sound opinion in doubtful cases, and even they may err on either side. A detailed consideration of this and other points regarding the relation of tonsillar infection to arthritis has been well brought out in a recent article by Lillie and Lyons.<sup>4</sup> The evidence adduced by a large number of cases in this series has clearly indicated, as pointed out, an impressive independence of focal infections at large, on the part of arthritics at this age as compared with older subjects. On the other hand, it must be granted that the conservative step in a refractory case is the removal of focal infection, and the apparent normality of the tonsillar tissues at the hands of any observer is not unfailing evidence that the tonsils are not acting as focal agents. It is difficult to steer a mean between these extremes. It is probable that for practical purposes it is wiser to regard the relative independence of focal infections shown by these young subjects as an academic consideration, and to regard possible foci of infection as causative agents until proven otherwise.

In thirty-four cases a culture study was made for *Streptococcus hemolyticus* following tonsillectomy. Twenty-one cases, or 62 per cent, were positive for *hemolyticus*, and thirteen cases, or 38 per cent, were negative for this organism.

The removal of dental foci played an important rôle also, although our figures show that dental foci were represented in fewer numbers, namely, 33 per cent of all cases, in contrast with 52 per cent of all cases showing tonsillar foci. It seems fair to say, that clinical observation substantiates the relative importance indicated by these percentages. Improvement may be marked after attention to either, but was rather more striking in the series in relation to tonsillectomy. This may easily be explained by the fact that dental foci, unless multiple, are actually smaller.

Our figures show that genito-urinary disease afforded only a small percentage of the foci met with, and, from the clinical standpoint, in only about two of the last 150 cases studied could such infection be found to bear any real relation to the arthritis. There is, therefore relatively little necessity to emphasize treatment of genito-urinary conditions as part of the treatment of arthritis as a whole among soldiers,

a consideration which would have importance in making provision for the care of larger numbers of arthritics were the war still in progress<sup>7</sup>

#### NONSPECIFIC PROTEIN INJECTIONS

It was demonstrated twenty-five years ago that the course of typhoid fever could be influenced favorably by the subcutaneous injection of killed typhoid organisms, or even pyocyaneus bacilli in the form of a vaccine. Since then other pathologic conditions have been treated by vaccines on this principle but only within the past five or six years has it been appreciated that the beneficial effects following the injection of foreign protein may be the results of a nonspecific immunologic reaction. Miller and Lusk<sup>8</sup> first suggested the treatment of arthritis by means of nonspecific protein injections and definite benefit is known to follow these measures in certain types and proportions of cases of arthritis at large but the method as a whole is in its infancy and its basis of action is as yet a matter for speculation. It is generally agreed that this form of therapy, as applied to arthritis, achieves its best results in the acute forms: subacute and chronic arthritis responding less readily, in the order indicated. The cases in the present series to which this treatment was given belonged for the most part in the chronic category for the reasons elsewhere mentioned and opportunity to use the treatment where benefit was most likely to result was infrequent. The method is generally regarded as being free from danger but Thomas<sup>9</sup> has reported several untoward results and the work of Longcope suggests the possibility of producing nephritic lesions by repeated protein intoxication.<sup>10</sup> The reactions which accompany treatment along these lines are generally unpleasant and Snyder has reported gastric hemorrhages and mild hematemesis. Cole and Miller and Lusk, have cautioned against the indiscriminate use of these measures, and Jobling has emphasized the dangers which may follow large injections. Opinions differ as to the size of the doses to be administered and Snyder advises beginning with small doses of from five to ten millions. Miller advises beginning with seventy-five millions<sup>11</sup> and in a recent comprehensive study of the changes in the blood

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5 I am indebted to Capt. George G. Smith M. C. U. S. Army, chief of the genito-urinary service at U. S. Army General Hospital No. 9, for his helpful analysis of this phase of the subject.

6 J. A. M. A. 66:1756 (June 3) 1916.

7 A bibliography will be found in "Clinical Report of Nonspecific Protein Therapy in the Treatment of Arthritis" by R. G. Snyder: Arch. Int. Med. 22:240 (Aug.) 1918.

8 J. A. M. A. 69:770 (Sept. 8) 1917.

9. J. Exper. M. 18:678 1913.

9a Personal communication.

following such therapy in ten cases of arthritis, Cowie and Calhoun<sup>10</sup> used doses of one billion without any reported ill effects

In view of the conditions, however, under which the subjects of the present study arose, it was believed safer and wiser to begin with a low average figure. The army typhoid vaccine was accordingly used in an initial dose of twenty-five million, the second dose, when given, being fifty million and the third, seventy-five million. Nineteen patients received nonspecific protein injections in a vein of the arm\*. Of these, seven were definitely improved, ten were unimproved and in two the results were uncertain. Of the seven improved, two were apparently cured, and of those unimproved, one patient was apparently made worse. Some of the patients receiving protein injections desired a second and even a third dose. This was true in one case in which great benefit followed the treatment, and in another in which only slight benefit accrued. A rather larger number of patients refused a second injection and nearly all the patients suffered a pretty severe subjective reaction. In slightly more than one-half of the instances, the temperature rose to almost a uniform height, from 103 to 104 F.

Ten of these cases were followed in respect of the blood count<sup>11</sup>. In the first seven cases, the full blood counts and differentials were made by Lieut Leslie N. Gay, M. C., to whom obligation is expressed for the care exercised. The remainder were made under the critical direction of Lieut J. W. Sherrill, M. C., director of the general laboratory, U. S. Army General Hospital No. 9. A full and differential blood count was made immediately before the injection, during the height of the reaction, and again twenty-four hours later. In a few instances, a count was made shortly after the injection, before the reaction had achieved its maximum. This series showed the usual picture of an initial leukopenia followed by a sharp leukocytosis, during the reaction, which averaged 16,470 leukocytes. The degree of leukocytosis apparently bore no relation to the leukocyte count before injection. Twenty-four hours after the injection, or after the subsidence of fever, the leukocyte count showed no important change from its original level, in four cases being slightly lower and in seven cases slightly higher. One patient had a leukocytosis of 11,400 during the reaction, and a delayed rise up to 30,000 twenty-four hours after the initial dose, although the fever had reached its height of 102.5 F. four hours after injection. Forty-eight hours after injection the leukocytes were practically at their former level. One patient in this series showed no leukocytosis either during the reaction or twenty-four hours later after dosage of twenty-five million organisms.

<sup>10</sup> Arch. Int. Med. 23:69 (Jan.) 1919.

<sup>11</sup> To save space the tables are omitted.

\* Mostly with the collaboration of Capt. Louis A. Levison, M. C. U. S. A.

In general, the series showed an absolute as well as a relative rise in the polymorphonuclears and a corresponding fall in the small lymphocytes. In one case, at the height of reaction, eight hours after inoculation, the differential count showed a decrease in the percentage of small lymphocytes compared with the formula before injection, and twenty-four hours after injection the differential count showed a marked decrease in the small lymphocytes but a great increase in the large lymphocytes.

Blood counts in this series, as a whole, showed, therefore, correspondence with the usual experience in this regard. In none of the smears examined were any pathologic cells seen, and both platelets and red cells were apparently normal. This is at variance, as far as it goes, with the carefully studied series of ten cases reported by Cowie and Calhoun,<sup>12</sup> who describe many kinds of atypical cells, but this difference may be due to the very much larger dose of typhoid vaccine which they employed, one billion as compared with an initial dose of twenty-five million, and to the fact that they made hourly counts.

It is important and interesting to note that although nonspecific protein injections in the form of typhoid vaccine are of some benefit, within limits, on diffuse groups of arthritic cases, particularly the acute and subacute, the subcutaneous injections, as practiced routinely in the army camps on the incoming draft, have been without effect to prevent rheumatoid disabilities. Inasmuch as these subcutaneous injections were always at least three in number, and inasmuch as the febrile rise and malaise following them are common experiences, it seems that there must take place, at least in a modified degree, some of the systemic reaction which follows intravenous therapeutic injections. Furthermore, owing to loss of records or other causes, forty-six patients had received more than the regulation three doses of prophylactic typhoid injections (11.5 per cent of the whole series), some men received as many as fifteen injections of the typhoid vaccine during their recent army service prior to the onset of the arthritis. It seems reasonable to deduce, therefore, that there is no prophylactic effect as regards arthritis from nonspecific protein administered subcutaneously, even after repeated dosage.

The rationale of nonspecific protein injection, when followed by beneficial results, has never been explained. It is well known to critical students of arthritis, that agents which profoundly disturb the existing conditions of life, such as the roentgen ray, radium, probably thyroid extract, and even such factors as excitement, a fatiguing journey, etc.,

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12 Loc cit

may be followed by periods of benefit. Some of these agents, at least, are known to stimulate the body metabolism as a whole and to induce increased catabolism.

It is also clear that a lowered intake of food may be followed by unquestioned benefit in a definite proportion of cases. This is graphically exemplified at times, as in several cases of this series (Case 53, Mrs. K., Case 52, Lynch, see "Dietary Consideration" and "Clinical Abstract of Cases Studied"), by the period of enforced starvation following such operations as tonsillectomy, or abdominal section. Under these conditions, catabolism runs ahead of anabolism and the body draws on its store of glycogen. The difficulty in the utilization of carbohydrate by the arthritic has been sufficiently developed in the chapters on "Blood Sugar" and "Dietary Considerations." There is other evidence to indicate that carbohydrate is caught up in some important way in the pathology of this disease.<sup>13</sup>

Barr and DuBois<sup>14</sup> have shown that the respiratory quotients during the chill of malaria suggest rapid combustion of glycogen stores during the violent muscular exercise of shivering. Attention has been drawn by Cowie and Calhoun to the fact that the characteristic malarial chill is probably an example of protein intoxication and reaction. There is every reason to believe that the same rapid combustion of glycogen takes place during a severe reaction from nonspecific protein. In view of the evidence grouped under these heads, it seems possible that the benefits from protein injection in arthritis may, in part, result from the heightened metabolism accompanying the marked febrile rise with consequent combustion of available carbohydrate. A factor contributory to this may be the incidental low food intake which accompanies the usual malaise of twenty-four hours or more. That this is the whole explanation can hardly be believed, that it supplies some of the contributory factors seems probable.

#### DIETARY CONSIDERATIONS

Experience in civil life with refractory forms of arthritis, has indicated a definite relationship in certain types of cases between the intake of food, on the one hand, and the incidence and perpetuation of the symptoms of chronic arthritis on the other. This relationship can best be illustrated by the fact that in certain cases of arthritis, not amenable to other therapy, the patient can be influenced greatly for the better or relieved of all symptoms by a sharp curtailment of the food intake as a

<sup>13</sup> See section on Creatin, also, Pemberton, R. *Am J M Sc* **43** 678 (May) 1917.

<sup>14</sup> *Arch Int Med* **21** 627 (May) 1918.

whole. Such a reduction can for purposes of discussion be considered in terms of the total calories involved, but evidence at hand has indicated that the carbohydrates may be the most concerned of the three foodstuffs. It is not intended to set forth here the observations forming the basis for this conclusion, as these have been elsewhere reported.<sup>13</sup> Experience in this connection, however, formed one of the influencing factors in determining the lines of attack on the present problem as a whole, and afforded one of the several lines of therapy undertaken in this series. Several instances will be cited in detail because of the further evidence they afford of the practicability of these methods, and of certain other points of interest relating to the nature of the present problem. As mentioned under the opening paragraphs on "Treatment," the number of patients treated by dietary means was smaller than the number of arthritics in this series would suggest, *a priori*, as available to any measure. The factors which made for other and simpler forms of treatment for this group, however, have been emphasized sufficiently. It has been pointed out in previous contributions, that treatment by these dietary measures should be reserved almost exclusively for those cases which are demonstrably not caused by infectious foci, cases in which the removal of foci is contraindicated, cases not accompanied by undernutrition, anemia, etc., and, in short, for that group of cases in suitable condition which has failed to respond to other measures. The evidence indicates that therapy along this line achieves its result primarily more by catering to a weakened function, than by removing the cause of that weakened function, although in the end that function may by these means be improved or restored to normal. It is, therefore, essentially an unsound policy to attempt relief of symptoms by dietary control in the presence of the demonstrably removable cause of these symptoms. Apart from this, dietary procedures of whatever kind, and particularly in the present connection, involve much cooperation on the part of the patient and considerable time, for which reason, even under the condition of civil life when patients are often willing to make any and all sacrifices to obtain relief, this form of therapy is to be employed only after full consideration. On first analysis it would appear that the conditions of a military hospital would insure control of the patients, with consequent cooperation from them far in excess of what might be expected in civil institutions, but experience has shown that this is not the case, except in respect of clearcut objective procedures, such as operations and the like which can be carried out with the efficiency of a military command. The youth of most of the patients, the shorter duration of the disease, the fact that these subjects had not suffered invalidism to



that degree which makes them willing to undergo protracted sacrifice, the loss of morale resulting progressively from treatments in many hospitals on their way back from the front, with small resulting benefit, all added cogency to the reasons mentioned for withholding these measures until clearly indicated. There can be no doubt, however, of the results achieved in this series in some selected cases and the application of these measures to the problem in hand can probably be best illustrated by a recital of a few of them, following this with a consideration of the points developed and a general discussion.

The undesirability of approaching the whole topic from too academic a standpoint, and of adding to the number of hospital days, was kept constantly before us. In carrying out the dietary measures here recorded, the effort was made to obtain results in the quickest manner, although it was appreciated that the opportunity for interesting contrasts in results was often thereby renounced. Thus, it will be noticed in the diets administered on the principle of a lowered intake, that not only were the calories reduced, but the proportions of the foodstuffs believed to be most advantageous were provided, notwithstanding that further data are desirable on the rôle played by the three foodstuffs uninfluenced by conditions of low feeding as a whole.

CASE 1—Robbins, aged 25 years, a lieutenant in the infantry, had suffered from an attack of inflammatory rheumatism nine years previously. After experiencing some disability in one shoulder for more than two months, apparently induced by bayonet drill, he was admitted with a painful and swollen left ankle to the base hospital at Camp Lee whence he was transferred to U S Army General Hospital No 9. Capt W W Gailey, Jr, chief of the nose and throat department at U S Army General Hospital No 9, reported that he did not think it possible that the tonsils could serve as foci of infection. Therefore, they were not removed and examination of the sinuses, teeth and genito-urinary tract proved conclusively negative. The patient had taken at one time as much as 90 grains of acetylsalicylic acid per day without relief. He was seen November 24 in consultation with Lieut-Col J C Gittings, chief of the medical service, and the conclusion was reached that he was not improving, but it was decided to wait another week in order to make sure of this. December 3 it was agreed that more active steps should be taken and he was placed on a diet. It was also agreed that any change noted could properly be ascribed to the new regime established.

Observations of the food intake of this officer for a period of about a week showed that he was ingesting an average of about 3,750 calories per day, which included about 700 calories from candy, of which he was very fond. Of this food intake about 12 per cent came from protein, about 29 per cent came from fat and about 50 per cent came from carbohydrate<sup>14</sup>.

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14 As mentioned in previous publications, it has been found convenient to estimate food values by reference to "Food Values," Edwin A Locke, and except where the data for any given foodstuffs could not be found, these tables were used by the dieticians in charge of food estimated or prepared on the arthritic service.

December 3, he was placed on a diet of 2,051 calories, of which about 10 per cent came from protein, 52 per cent came from fat and 38 per cent came from carbohydrate

BREAKFAST		Calories
1 apple	150 gm	72
1 egg	50 gm	83
Bread	60 gm	162
Butter	15 gm	120
Sugar	20 gm	80
Milk	60 c c	39
Coffee		

LUNCH		
Bouillon	120 c c	
Lettuce	40 gm	
Mayonnaise	1 t'blespo'n	187
String beans	100 gm	17
Bread	30 gm	80
Butter	10 gm	80
Orange	250 gm	95
1 egg	50 gm	83

SUPPER		
Steak	50 gm	143
Bread	60 gm	160
Butter	15 gm	120
Tea		
Sugar	20 gm	80
Milk	60 c c	39
Beets	100 gm	40
Lettuce	40 gm	
French dressing	2 t'blespo'n	298
1 apple	150 gm	72

Total calories		2,051 <sup>1</sup>
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Four days later he could move around without crutches, having been practically bed-ridden before. After eleven days the improvement was marked and he had no conspicuous ache in the hip, shoulder or elsewhere, the residual points of tenderness being few.

After this abrupt change in his condition there followed a gradual and progressive betterment. Except for occasional fluctuations, which grew fewer in number and less severe, and changes in the distribution of involvement, this case showed, as do most cases which improve along these lines, amelioration of the original picture until few and finally no joints were involved. This officer lost 10 pounds in weight and finally reached an equilibrium. His food intake was then increased by one egg, and finally by olive oil to bring his calories up to about 2,500, of which about 8 per cent came from protein, 62 per cent came from fat and 30 per cent came from carbohydrate. At this point he was playing golf and walking about seven miles a day in apparently

<sup>15</sup> It is to be appreciated that trifling differences occur in the caloric values quoted for various articles of food, according to the table from which these values are obtained. It will, therefore, sometimes happen that there may be an apparent discrepancy of a few calories between the numbers indicated in the text and the summation of the detailed diets, but these are within the inevitable error in the administration of mixed foodstuffs at large.

perfect health. Because of his desire to insure maintenance of his improvement, he was allowed to remain at the hospital until May, having by that time been essentially well for two months, so that opportunity was afforded to observe not only the original improvement but also its establishment.

The sugar tolerance displayed by this patient on four occasions is illustrated by the two composite curves on Chart 9 (page 268). The first two curves were taken during ill health and showed a definite, although moderate elevation, the last two curves were obtained during convalescence and good health, respectively, and gave essentially normal values. They illustrate that the sugar tolerance may return to normal, coincident with improvement of the individual by restriction of diet. Observations were also conducted on the basal metabolism and blood and urinary creatin and creatinin of this subject.

In contrast to this case is the following:

CASE 2—Sergt Lowe (Case 14), aged 42 years, had been invalided for two years from progressive polyarthritis, involving all joints, without any considerable limitations in their range of motion, if cautiously and slowly carried out. This case was apparently of the so-called dry or fibrous type, characterized by few roentgen-ray changes even after a long period, although these were demonstrable along the phalanges of the hands. This soldier had had no less than thirteen different kinds of therapy without avail<sup>16</sup>. His food intake averaged about 2,459 calories, but after sharp reduction of his diet in varying degrees for twelve days apparently no benefit accrued, and efforts along this line were discontinued.

What might have happened had a restricted diet been longer administered cannot be stated, but experience with other refractory cases of this series at least suggests that a combination of treatment on this basis, supplemented by other measures, might have yielded more favorable results. One of the lessons learned from this series is that combinations of treatment will sometimes effect improvements, if a favorable basis be established first, when single lines of effort fail, as is shown by Case 3.

CASE 3—Sergt Hayes (Case 6), aged 29 years, was invalided for two years. He presented widespread deformity of the phalanges of both hands with peri-articular soft tissue involvement, ankylosis of the right wrist, great tenderness, boggyness, swelling and redness of the left wrist. At the outset there had been involvement of the feet, but this had disappeared. The teeth and genito-urinary tract were entirely negative. A tonsillectomy was performed December, 1918. Eight weeks later there was no improvement to be detected. It was then decided to place him on a restricted intake of food. Observation of this soldier's ingestion of food for eleven days gave an average intake per diem of 3,000 calories, of which about 15 per cent came from protein, 39 per cent from fat and 46 per cent from carbohydrate. He was then placed on a diet of 2,051 calories, of which about 8.5 per cent came from protein, 50 per cent came from fat and 41.5 per cent came from carbohydrate, beginning January 11.

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16 See appendix of case histories.

## BREAKFAST

		Calories
1 apple	150 gm	72
1 egg	50 gm	83
Bread	30 gm	81
Butter	15 gm	120
Milk	60 c c	40
Sugar	20 gm	80
Coffee		

## LUNCH

Bouillon	180 c c	
1 egg	50 gm	83
String beans	100 gm	17
Lettuce	40 gm	
Mayonnaise	1 tablespoon	187
Bread	30 gm	81
Butter	10 gm	80
Orange	250 gm	96

## SUPPER

Steak	50 gm	143
Beets	100 gm	40
Lettuce	40 gm	
French dressing	2 tablespoons	296
Oil	1½ tablespoons	161
Bread	30 gm	80
Butter	15 gm	120
Sugar	20 gm	80
Milk	60 c c	40
1 apple	150 gm	72

Total calories

2,052

Twelve days later there was unquestionably less tenderness and swelling and probably greater freedom of movement in the left wrist than at any time during the two months of observation, and there had also been for nine days distinctly less aching, of which there was at times entire absence. This improvement was noted by many observers, and was maintained with some further improvement until February 2. About this time his condition became stationary after an improvement of about 50 per cent, and remained so for some weeks under the same conditions. In this period he had been made to lead a very quiet life and had lost about 3½ pounds in weight. In the effort to hasten progress, he was given two days of sharp fasting (March 7 and 8) on 857 calories without appreciable results. This period was started by a dose of calomel which upset him considerably and may, in some degree, have complicated the issue. After subsidence of his gastro-intestinal disturbance, he was given unrestricted diet until March 23 when he was placed on about 1,400 calories, plus potassium iodid, 5 grains, three times daily, cod liver oil emulsion, 50 per cent, 8 c c three times daily.

No further benefit resulted from this by April 4, although the improvement was well maintained. He was then put on a full diet for three days, and on April 9 he was again placed on the original diet of 2,050 calories, plus cod liver oil and potassium iodid. To this régime a daily sweat of fifteen minutes in a hot pack was added. After about two weeks the hot pack was substituted by a whirlpool bath, with water at about 100 F for the left arm and this was also productive of profuse general perspiration. The swelling undoubtedly greatly subsided in the left wrist and he confessed to feeling much less tender on palpation. May 8, under maintenance of this régime, the left wrist had assumed a practically normal appearance and his condition could conservatively be estimated as improved at least 90 per cent.

This case illustrates that after the institution of a reduced diet with evidence of progress as a result of the removal of a "metabolic load," the patient's condition may then remain in statu quo but that other agencies acting on such a basis may then suffice to influence greatly the residual arthritis, although unequal to this end alone

CASE 4—Miss H, army nurse corps, was taken sick overseas in January, 1919, and invalided home with pain, supposedly of sciatic nature on the right side, marked disability of the left shoulder and some disability of the right hand. She was admitted to the hospital January 25, complaining of the above symptoms, and mostly of aching at night. Examination of her teeth, nose and throat revealed no surgical foci, the tonsils being particularly inconspicuous and apparently innocuous. No gynecologic examination was made. In view of her previous robust health and hard work in the army hospitals, it was believed that rest would relieve her symptoms, but after two months, during which she had had a sick leave, she was worse than on admission, and it was decided to place her on a limited diet.

Estimation of her food intake for a few days revealed that she was eating at least an average of 2,000 calories, about 17.5 per cent of which came from protein, about 40 per cent came from fat and about 43 per cent came from carbohydrate. As she was fond of eating between meals, however, it is probable that her intake occasionally went above this point. In view of these figures, however, April 18 she was placed on the following fixed diet of approximately 1,700 calories, distributed as follows: 10 per cent from protein, 62 per cent from fat, and 28 per cent from carbohydrate.

BREAKFAST			Calories
1 orange	250 gm		96
2 eggs	100 gm		166
Bread	30 gm		81
Butter	15 gm		120
Coffee			
Milk	60 c c		40
LUNCH			
Bouillon	180 c c		
Lettuce			
Mayonnaise	1 tablespoon		187
String Beans	100 gm		17
1 apple	150 gm		72
Bread	30 gm		81
Butter	10 gm		80
SUPPER			
Steak	50 gm		145
Bread	30 gm		81
Butter	15 gm		80
Carrots	100 gm		13
Lettuce			
French dressing	2 tablespoons		295
1 orange	250 gm		96
Milk	60 c c		40
Tea			
Bouillon	180 c c		
Total calories			1,694

April 23, she said that she felt better than at any time since admission to the hospital and her knees and hips were free from pain. April 24, cod liver oil emulsion, 50 per cent, U S P, 8 cc three times daily, was added. Progress was steady until May 4, when she suffered an exacerbation coincident with a protracted period of wet weather, which affected many arthritics on the service. Despite this function apparently improved because May 13, her arm could be raised higher than at any time to date almost vertically, and toward the end of the month she left the hospital having lost about 1 pound in weight, feeling not at all weak, able to walk three or four miles at a time, and, by her own statement as well as by the objective evidence of function in her left shoulder, substantially improved.

It is to be noted in this case as in others previously reported, that weight was essentially maintained and that activity was possible on a caloric intake which would generally be regarded as only slightly above the minimum figure for such conditions. This patient was of large and solid build, without being fat and she experienced little or no difficulty from her limited intake other than being deprived of the pleasures of the table. People differ considerably in respect of the way in which they tolerate a diet restricted to this degree, not only from the mental, but also from the physical standpoint. It was possible in this case to maintain this level successfully and easily, whereas with certain soldiers such a régime proved to be difficult or impossible. This patient was instructed to maintain conditions as they were for two months and then slowly to add to her intake little by little, according to a schedule given her, as explained in previous contributions.

CASE 5—Lieut. Lynch (Case 52) aged 33 years had had one previous attack of arthritis and was admitted to the hospital after about six months of invalidism affecting the spine, knees and particularly the feet and heels, which were swollen and extremely tender at the insertions of the Achilles tendons. Some limited benefit had followed removal of an abscessed tooth but five months later no further improvement had taken place. Tonsillectomy was performed April 5 on general principles, although no other indications were seen by several observers, and the tonsils proved negative for *Streptococcus hemolyticus*. The experience of this patient on the two days following the tonsillectomy, during which he felt a marked improvement, coincided with observations frequently made and published elsewhere,<sup>17</sup> that during the postoperative period of incidental low feeding or starvation there often ensues a noteworthy improvement of rheumatoid symptoms. Following the two days mentioned, this officer grew progressively stiff and painful in respect of his joints, and five or six days after the operation was feeling as badly as before. This experience brought prominently into consideration the probable influence of diet in this particular case and on consultation with Lieut-Col. J. C. Gittings, chief of the medical service it was decided to give him the benefit of the doubt. It was further agreed that any sharp change resulting from a dietary régime could properly be ascribed to it.

An estimation of his average intake of food showed that it approximated about 2,600 calories per diem, of which roughly 9 per cent came from protein,

<sup>17</sup> Pemberton, R. Am J M Sc 43 678 (May) 1917

41 per cent from fat and 50 per cent from carbohydrate. Accordingly, on April 16 he was given one day of sharp fasting, his only food consisting of bouillon, coffee and bran biscuits. April 19 he was placed on the following diet of 1,641 calories, of which about 10 per cent came from protein, 62 per cent from fat and 28 per cent from carbohydrate.

## BREAKFAST

		Calories
1 orange	250 gm	96
2 eggs	94 gm	156
Bread	30 gm	81
Butter	15 gm	120
Coffee		

## LUNCH

Lettuce	40 gm	
Mayonnaise	1 tablespoon	187
String beans	100 gm	17
1 apple	150 gm	72
Bread	30 gm	81
Butter	10 gm	80

## SUPPER

Beefsteak	50 gm	143
Bread	30 gm	81
Butter	15 gm	120
Carrots	100 gm	18
Clear bouillon	180 c c	
Lettuce	40 gm	
French dressing	2 tablespoons	296
1 orange	250 gm	96

Total calories

1,641

April 20 there was less tenderness under the Achilles tendons of both feet and progress was fairly consistent from that date. About April 24 he developed a rheumatic iridocyclitis of the left eye. On this date he could walk in his bare feet and even rise on his toes, which he could not do before the diet was instituted. He could walk quite freely in his shoes and made all movements more easily. He said that he had not made so much progress at any previous time during a comparable period. The iritis ran a painful course of about ten days, exacerbations of pain being occasionally controlled by acetylsalicylic acid. April 24, cod liver oil, U S P emulsion 50 per cent, 8 c c, three times daily, was started.

The end-result in this case was that the iritis subsided entirely and he evidenced an improvement in his rheumatoid symptoms subjectively and objectively. The ocular pain had for a day or two prevented his eating, to compensate for which he was placed for two days on an unrestricted house diet, after which, with the patient's willing cooperation, he returned to the restricted diet of 1,641 calories.

This officer had of necessity led a very inactive life while on this low food intake and lost no weight. He disappeared from observation owing to the closure of the hospital, but the therapeutic benefits indicated during the period described could not be ignored.

It is of interest to note that in another less severe case on the arthritic service not under dietary treatment, the patient suffered an equally severe iridocyclitis of one eye during practically the same

period Within about the same month, four other cases of apparently rheumatic iridocyclitis also presented in the institution among patients on other services

CASE 6—Private Oberg (Case 22), aged 24 years, had had at least six previous attacks of diffuse severe arthritis dating from early childhood At the time of enlistment in the medical corps, March 18, he was a premedical student and was accepted for full duty During training he experienced some trifling stiffness which disappeared, and he performed full duty overseas in a base hospital until the end of August, 1918, when he went to bed with fever, great pain and limitation of function in his hips and left shoulder, being unable to walk The onset had been gradual, extending over some weeks, and from the date mentioned there was no important change in his condition until he was admitted as a litter case to General Hospital No 9, Jan 21, 1919, after being five months on his back

He presented complete fixation of both knees and markedly lowered function of the left shoulder, accompanied by roentgen-ray evidences of marked erosion of the greater tuberosity of the left humerus and atrophic arthritis of the knee During his invalidism overseas, he had received without benefit, antistreptococcus serum in September, 1918, as a therapeutic measure in lieu of non-specific protein in the form of typhoid vaccine He had apparently a rather severe reaction, with fever, chills and increased pain He stated that he had also had in civilian life, during an attack, an injection of a "rheumatic serum" without benefit On admission, he was slightly better than he had been two months previously, but the difference was trifling and his incapacity was complete

Examination of the genito-urinary tract was negative Roentgen-ray examination of the teeth showed one small apical abscess, and there was division of opinion as to whether or not his tonsils were entirely innocuous or whether they were diseased and constituted a possible focus The apical abscess was removed without apparent influence Because of the ankylosis of the hips and spine, the consequent difficulty of tonsillectomy in this case, the doubt as to the existence of tonsillar infection, and the fact that it was believed that a radical effort was justified in the attempt to avoid fibrous or bony union in the hips and knees, this soldier was placed on a rigid régime<sup>18</sup>

On the evening of February 26, he was given a small dose of calomel followed the next morning by one dram of Rochelle salts During February 27, 28 and March 1 and until noon of March 2, he was placed under conditions of essential starvation, being allowed nothing more than bouillon, black coffee and bran biscuits February 28, consultation with Major Cleary revealed that there was a small amount of increased motion of the thighs and of the knees, with apparently somewhat less pain For the first time in the observation of Major Cleary and myself, there was rotation of the left thigh on the pelvis February 30, he was given 857 calories per day made up as follows

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<sup>18</sup> This case was followed closely by Major E W Cleary, head of the orthopedic department and later chief of the surgical service at U S Army General Hospital No 9 His dispassionate and cordial assistance was of great value throughout the course of these studies particularly in connection with this case It was only through the cooperation of Major Cleary and his assistants that analysis could be attempted successfully of the many complicated cases of sacroiliac, vertebral and diffuse lumbar disability which presented It is a pleasure also to record the cooperation afforded by the other officers of the orthopedic service on the many occasions where patients were transferred or jointly treated by both departments



BREAKFAST			Calories
1 egg	50 gm		83
Butter	15 gm		120
Bread	15 gm		40
Coffee			
11 a m, black coffee			
LUNCH			
Bouillon	180 c c		
Lettuce	30 gm		
French dressing	1 tablespoon		148
Bran biscuit			
Cabbage	50 gm		3
3 p m, black coffe			
SUPPER			
Bouillon	180 c c		
1 egg	50 gm		83
Bread	15 gm		40
Butter	15 gm		120
Lettuce	30 gm		
French dressing	1 tablespoon		148
1 apple	150 gm		72
Total calories			857

March 6, Major Cleary demonstrated that both thighs could be flexed on the pelvis to about thirteen inches from the bed, with rotation of both hips, internal and external. The right knee could be flexed relatively freely, and flexion of the left knee was increased. March 7, the acetone reaction was distinct, but not great in both urine and blood plasma, the blood carbon dioxide was 50, and he evidently had a mild acidosis.

March 8 the diet was increased by one egg and 10 gm of butter, 163 calories in all, making a total of 1,020 calories. March 11, the patient was stood on his feet with the assistance of Major Cleary, placing his whole weight on his legs and standing upright except for the kyphosis. He moved the legs slightly as in walking and rocked the body to and fro without pain. The opinion was reached that the acute process was subsiding and that the present limitation and disability were residual. In view of the improvement and existence of a moderate acidosis, it was decided to increase the diet largely in preparation for another period of low feeding. He was placed on an unrestricted diet, which yielded about 2,700 calories, for twenty-four hours, after which, March 13, at supper he was placed on a diet yielding 1,534 calories made up as follows:

BREAKFAST			Calories
Coffee			
1 egg	50 gm		83
Bread	30 gm		41
Butter	20 gm		160
1 apple	150 gm		72
LUNCH			
Bouillon	180 c c		
Lettuce	30 gm		
French dressing	2 tablespoons		296
Cabbage	50 gm		3
Butter	10 gm		30
Bran biscuit			
Black coffee			
1 egg	50 gm		83

SUPPER		
Bouillon	180 c c	
1 egg	50 gm	83
Bread	30 gm	81
Butter	20 gm	160
Lettuce	30 gm	
French dressing	2 tablespoons	296
1 orange	250 gm	96
Total calories		1 534

March 14 his acidosis had disappeared. He continued to do well on this diet until about March 25, during which period he frequently walked with assistance, progressively better, his movements being limited only in range of action and the power with which they could be executed. At about the date mentioned, he developed pain in the left chest with increased disability of the left shoulder. After being watched for two days, it was believed that this disturbance might be pleuritic, with undesirable consequences, and he was placed on an unrestricted diet. There were very slight fever and signs of a small left sided effusion. The leukocytes numbered about 12,000, the polymorphonuclears numbered about 51 per cent, and the proportions of the other blood elements appeared to be normal. The pleuritic condition subsided. March 31 he developed slight effusion and tenderness of the left knee and April 1 there appeared edema of the left thigh, tenderness above Poupert's ligament, evidence of moderate left femoral thrombosis with fever and a cylindrical tender mass in the upper femoral region. This condition slowly subsided and April 8 it was clear that despite these two exacerbations, motion in the hips and knees was well preserved or even increased. April 15 the following note was made by Major Cleary: "Examination shows that edema of the left leg has decreased definitely, and tenderness has almost entirely disappeared. The range of motion of both limbs gradually gained by the patient up to the time of exacerbations is entirely retained. Within this range, motion is more free than it has been before. The patient moves his limbs with a confidence which indicates much less fear of causing pain. The improvement in this case has been coincident with, and in my opinion due to, the strict dietary restrictions imposed."

From this time on, the patient ingested for the most part an average of about 1,800 calories per diem. April 20, 22, 23 and 24 he again walked across the room with assistance, feeling greatly encouraged at his large increase of potential.

In view of the prospective closure of the hospital and the doubt that still remained as to whether his tonsils constituted a focus of infection, it was decided to remove them as a prophylactic measure. This was done April 27 and April 30 there developed edema of the uvula with a temperature of 101 F. These symptoms subsided in a few days. After tonsillectomy the right hip suffered a slight exacerbation, being more sore than at any time since improvement began. The tonsils showed *Streptococcus hemolyticus* in small numbers and were small and necrotic.

It was plain from a dispassionate survey of this case that the régime instituted resulted in abrupt return of motion in previously ankylosed hips and knees, and the patient, from having been utterly bed-ridden, was able to get out of bed and into bed without assistance, to walk freely with crutches, even getting around with a cane and the support of objects in the room. There was no doubt of his betterment and prospective further improvement, and he was reported as doing very well three months later. August, 1919.

As is fully described under the section treating of blood sugar, this patient had a very low sugar tolerance and the fact that the tonsils played a rôle as focal agents is indicated by the return to normal of his sugar tolerance after their removal. It is possible that an error was made in not removing them at the outset, but subsequent events indicated that his return of function was more rapid under dietetic treatment before his tonsils were removed than was increase of function (when he had already made marked improvement) after his tonsils were removed. As also indicated elsewhere, the persistent low sugar tolerance in this case, in the light of later events, afforded some evidence that all foci of infection had not been removed. It is to be noted that his improvement under dietary régime was emphatic, even in the presence of what was apparently focal and even causative infection. This case was highly illustrative of the abrupt and marked improvement which can be brought about in properly selected cases, even in the presence of long standing arthritis, amounting clinically to ankylosis. Whether the attacks simulating, respectively, pleurisy and phlebitis were referable in any way to the period of underfeeding cannot be settled definitely. It does appear, however, that they were rheumatoid in nature, and it is in line with my experience with other cases treated less radically in the same way, that, after a sharp initial improvement, there may ensue, at later stages, exacerbations at one or more sites which continue decreasingly until the patient is well established in convalescence. It is in this connection that unpleasant consequences might follow the application of low diets to patients the subject of anemia, inanition and the like. These exacerbations, however, in properly selected subjects, such as the present one, are no greater than occur in any event, they grow less frequent and severe, and they may be absent altogether. It is probably somewhat because of the contrast with betterment that they attract attention. This patient was treated by more heroic measures than I had exercised before, and it is not recommended that they be adopted without full deliberation, and only then in proper cases.

One of the conclusions developed, therefore, as the result of this experience in the dietetic handling of arthritis not amenable to other forms of therapy, is the fact that in certain cases the period of reduced diet may be advantageously ushered in by a short period of sharp fasting. There are limitations to the degree to which this may be pushed, notwithstanding occasional striking improvement at the outset, because too much undernutrition may retard rather than assist the later response, which must be sustained to be effective. Too much stress cannot be placed on the fact that only selected cases, patients in a state of good general nutrition, should be subjected to this initial procedure. The methods necessary to achieve permanent benefit along dietary lines

should not be adopted unless there be available experience with the confusing sequels of arthritis, which often simulate active disease, and experience with nutritional problems and the calculation of accurate diets. I have endeavored to point out elsewhere with all possible emphasis, that such procedures constitute a two-edged sword capable of evil as well as good, and likely to result as much in evil as in good unless appropriately applied.

The preceding experiences with diets should not be viewed as isolated observations. They should be interpreted as part of a considerable series of cases treated on the same principle under changing experimental conditions, as previously reported.<sup>13</sup>

In the subsequent light of the slow response of a number of cases to other measures, it is regretted that more patients were not so treated, but as already mentioned, this therapy was reserved for the most refractory types because of the time and cooperation required. It should never be resorted to alone in the presence of removable foci of infection. It affords a means, however, by catering to a weakened function, of reaching many cases that have responded to no other efforts, and it is clear that it can also be used to good effect, although only in properly selected cases, in conjunction with other measures.

In working with numbers much greater than make up this series, it is probable that one or two fixed, graded diets could be used to advantage, but the problem of the arthritic is an individual one, diagnostically and therapeutically, and much the same limitations obtain as would in attempting a similar control of diabetics.

In view of the fact that there was indicated by the nephritic test meals a slight retention of salt by the kidney, two patients were placed for periods of two weeks on salt-free intake, one as a therapeutic test, and the other partly for that purpose and partly to facilitate absorption of an edema of the leg, but no therapeutic effect on the arthritic process was observable in either instance.

#### LOCAL AND EXTERNAL MEASURES

As already mentioned, the subjects of this study showed a greater tendency towards recovery than do similar cases under civil conditions occurring in the later decades of life. Probably because of this, they also showed a surprising response to local and external measures, comprising chiefly baking, massage, hydrotherapy and electricity.

Many patients recovered entirely in spite of neglect that was probably unavoidable. Many on the way to recovery were hastened in their convalescence by the vigorous institution of local measures, particularly massage and baking. In some cases, benefit and symptomatic cure followed almost at once after a long period of invalidism. Many cases

gave clear evidence of benefit from such measures at hospitals established at the watering places of France and elsewhere, and there was no room for doubt that full utilization of these adjuvants was often productive of good. It was a matter of difficulty, however, to attach the proper importance to any or all of these agents. The single statement in regard to their utility that can probably be safely made is that they should be regarded as adjuvants rather than as the fundamental bases of therapy. These measures all have at least one element in common, the induction of hyperemia, and their field of application as previously mentioned is properly in cases which tend to recovery, cases of mild degree and cases in which the basis of convalescence is already laid. They can also be used with propriety in adding to the comfort of more severe refractory types in which, however, their curative effect is slight or absent.

If it were necessary to select one of these measures as that which alone could be applied, the first choice would probably be baking, on the one hand, because of the benefits to be derived, and, on the other, because of the relative ease of application by means of small portable units or home-made measures. This is particularly true in view of the etiologic rôle played by exposure in this series, and many subjects dated improvement from their return to conditions of warmth and dryness.

The application of massage to the subjective and objective disabilities consequent on "rheumatism" and arthritis is too widespread to call for much comment. Many of the sequels of arthritis are similar to those following trauma and other factors within the orthopedic field, and in this connection massage accomplishes some of its best results. The disability originating from contracted tendons, thickened capsules, etc., may so closely resemble, in respect of pain, that due to active arthritis per se, that the greatest skill is sometimes required to differentiate them. This field, however, is so familiar to qualified orthopedists, that it is unnecessary to enter on it at length except to emphasize the importance of interpreting properly the indications for and against massage. Probably one of the most common errors in treating arthritis is in the application of massage to a chronically but actively inflamed joint, thereby adding mechanical trauma. Deep massage to the large muscles was useful where they needed development and where locomotion was being encouraged.

It is, perhaps, pertinent to mention at this point that a desirable result achieved by any or all of the external measures above enumerated in the care of soldiers, was that of giving them the sense of being actively treated. In a disease of such chronicity, in which much time is sometimes required to demonstrate even the failure of a given line of

therapy, the importance of giving these men this satisfaction and of affording them at least momentary "bien aise" is not to be discounted. It is something of a commentary on the lack of systematized treatment of arthritis in general that many of these men had been through ten or fifteen hospitals and complained of having had no treatment of any kind, except rest in bed. Their satisfaction with these objective procedures when practiced at U S Army General Hospital No 9, brought this point to our notice, although a comparable satisfaction on the part of the public at large is common knowledge.

It was also difficult to place a proper value on hydrotherapy and the sweating or eliminative processes so frequently employed in the treatment of arthritis.

The available evidence suggests, as mentioned in the chapter on renal function, that the chief factors active in producing benefits under these conditions are those to which the sweats are incidental. In other words, raising the body or local temperature to a point higher than normal, results, in the former case, in increased metabolism, in the latter case it results in hyperemia and possibly locally increased metabolism as well. It is important, therefore, not to confuse cause and effect. It is entirely possible that other factors are operative, such as the changes in the fluids of the cell induced by diaphoresis, but this is independent of the question of elimination, *per se*. The possibility of benefiting certain patients by these measures, however, cannot be denied. The facilities available permitted only of the use of whirlpool baths for single limbs, together with the various general douches, and these were developed only shortly before the closure of the hospital. The local whirlpool baths were productive of good results and were generally enjoyed by the patients. They were much to be preferred to hot packs in bed and were also more easily productive of about as much free perspiration as followed the latter measures. Before the installation of whirlpool baths, however, hot packs were resorted to with some success.

It is probably even more difficult to estimate the alleged value of the various electrical treatments than is the case with any of the other measures mentioned. In so far as electrical therapy depends on the induction of muscular contraction, and in so far as it was depended on to raise the temperature of a part locally either by placing it in a bath or by passing the current directly through the part, the indications for its use were clear, and it supplemented other measures advantageously. Opportunity did not permit, however, of giving the attention necessary to weigh the benefits alleged to accompany other forms of electrotherapeutics. It is hardly to be doubted that the metabolism is importantly altered systemically as well as locally through various activities

of this kind, but this field needs study at the hands of critical clinicians together with coincident careful laboratory work in several directions

Of the measures above described as being useful in the treatment of chronic arthritis, electricity in its various forms supplies the greatest psychic influence to the individual. In this respect it plays a useful rôle in the therapy of a disease where chronicity, with resulting lowered morale, is so frequent. Provision for the care of a large group of soldiers the subject of chronic arthritis would probably be incomplete without inclusion of the usual standard electrotherapeutic appliances.

The indications for local and graded exercises were such as are common in orthopedic experience and were met in the usual way as far as the hospital facilities permitted. Outdoor exercise, such as walks and golf, played a limited rôle in the treatment of these men and was resorted to as soon as conditions warranted. It was highly useful in overcoming hospitalism, inducing free perspiration, developing weakened musculature generally, and in putting individuals in condition finally to assume the duties of an active life.

#### SUMMARY

The purposes for which the present effort was undertaken were three in number: (1) To treat as many soldiers who had arthritis as might be reached through one center established for this purpose, (2) to conduct intensive studies as to the nature of the disease and the best manner of treating it, (3) to consider critically those elements of the problem which have military application with the view of lowering the incidence of the disease, if possible, on the one hand, and, on the other, expediting the return of arthritics to duty, thereby contributing to the number of available men and to a reduction of hospital days and congestion.

The results of this effort can conveniently be grouped under two heads, (1) those of a more or less academic nature bearing on the pathology of arthritis, together with purely medical considerations along this line, and (2) those which concern chiefly the military aspect of the problem in relation to conditions of warfare. The results of the several lines of laboratory investigations undertaken have been sufficiently emphasized in respective chapters dealing with these topics to make repetition of these findings unnecessary. The outstanding facts concerning them will be summarized in the final conclusions.

The purely practical aspects of the question, in relation to the emergency created by the war, however, will bear further emphasis.

Statistical analysis has revealed, as indicated under that caption, that 36 per cent of the 400 patients presenting on the arthritic service

at U S Army General Hospital No 9, had had previous attacks of rheumatism. In contrast to this, only 7 per cent of 113 cases analyzed on the orthopedic service had had previous attacks of rheumatism, and these latter figures are borne out by statistics compiled by Capt. Bertrand Smith, M. C., chief of the Cardiovascular Department of U S Army General Hospital No 9, which indicates that in less than 6 per cent of 350 cases of functional cardiac disorder, was there obtained a history of "rheumatism" before admission. It is clear that something induced previous attacks of arthritis or rheumatic disability among the subjects of this study with a frequency five times greater than obtained among soldiers at large.<sup>19</sup> The thought is at once suggested that the incidence of arthritis in the army would be reduced by rejecting, at the time of an incoming draft, all men giving a definite history of arthritis or "rheumatism." That this would accomplish the purpose in mind is hardly to be doubted, but it would probably, at the same time, needlessly cut down the number of recruits.

In view of the fact that one outstanding tangible factor in the production of arthritis at large is focal infection, it would seem a justifiable recommendation, were the war still in progress, that recruits giving a definite history of previous attacks of a rheumatoid nature, should be segregated for careful analysis as to obvious foci of infection.

It would seem reasonable to be guided by the severity and frequency of the previous attack, rejecting absolutely extreme instances, and segregating for examination those of a milder nature. Although all recruits admitted to the army are supposedly examined as to their teeth, ears, throat, etc., this examination, in the nature of things, is not adequate to cover the point at issue. There is little doubt that routine analysis of a group segregated for the above purpose would reveal at the hands of qualified examiners, bearing this point in mind, an appreciable number of potential and causative surgical infections. Our statistics show that 73.25 per cent of all men admitted to the arthritic service were the subject of demonstrable surgical foci of infection. The possibility, therefore, that foci played a rôle in the etiology of arthritis among the 36 per cent of men having had attacks prior to their army service, is obvious.

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19 Organic heart disease is to be excepted. A personal communication through the courtesy of Captain Smith just quoted, indicates that of 150 patients with organic heart disease 42.9 per cent (64 cases) had had acute rheumatic fever either before or during military service. Of these 64 cases, 23.4 per cent (15 cases) had had no attack before entering the army. In other words, of 150 cases, 32.7 per cent (49 patients) had attacks prior to army service, a proportion slightly lower than in the case of arthritis (33.75 per cent). In point of fact, these two sets of statistics in some part cover the same field as many forms of organic heart disease are notoriously of "rheumatic" nature and origin.



Following the determination of focal infection in draftees who had had previous attacks of rheumatism, it would be possible, then, to anticipate the steps which became necessary eventually in the case of all soldiers in this series who had not recovered on admission to the hospital, namely, the removal of demonstrable surgical foci

A precedent in the recommendation of dental attention, when necessary, has already been pretty widely established on grounds of general prophylaxis alone, and the experience of the warring countries has shown that efforts at conservation of this nature would have added justification as continuation of the war made further demand on the available man power. The action here suggested constitutes a more critical application of an existing precedent to achieve a specific rather than a generic purpose. The degree of success which would follow institution of such measures could be determined only by experience, but that an important reduction in the incidence of chronic arthritis would be achieved by the specific application of these means is hardly to be doubted.

As the statistics show, 71 per cent of all foci were tonsillar (52 per cent of all cases), 45.7 per cent of all foci were dental (33.5 per cent of all cases). The tonsillar foci would necessitate an operation for their removal with consequent hospital days, and could await a time of election. The removal, however, of dental foci, which the statistics show were practically invariably abscesses at the roots of the teeth, could be accomplished in most cases without difficulty or delay. Genito-urinary diseases have apparently played such a small rôle in the etiology of the present series, that the importance of instituting analogous action in regard to them is not so great, although the same procedures could be followed.

The rejection of extreme instances and the examination and subsequent treatment of draftees giving a history of "rheumatism" and bearing surgical foci, would leave a group in which no infection could be demonstrated. It would seem justifiable, in connection with this group, to be guided solely by the severity and frequency of the previous attacks, rejecting from service those cases in which these factors were marked and accepting for service those men who were in apparent good health and had had no recent disability of this nature.

As mentioned in the opening chapter, the number of cases of chronic arthritis to be expected in an army of 4,000,000 men is so considerable, and is so substantiated in respect of numbers and severity by the studies herewith presented, that it must be concluded that chronic arthritis constitutes one of the outstanding medical conditions affecting the soldier in service, particularly under conditions of active

warfare in the field<sup>20</sup> It is probably fair to say, that the magnitude and importance of this problem have been somewhat overlooked in the emphasis placed on other, sometimes less considerable, conditions The problem from the purely numerical standpoint is not equal in size to that presented by the acute infectious diseases at large, particularly in the camps of this country, but it is to be remembered that, for the most part, the subjects of the acute infections recovered or died, a relatively small percentage returned to civil life incapacitated The subjects of arthritis, however, not only run a course exceeded in length by few conditions affecting large bodies of men, but carry into civil life, in regrettable proportions, conditions which incapacitate them for a long time or even result in permanent disability That they do better as a class than do cases of equal severity in the later decades of civil life does not remove the problem The impression was forcibly borne in on us in the course of these studies, that subjects of an arthritis of even moderate severity were often more incapacitated and for a longer time than were soldiers who had suffered an amputation The patient who has had an amputation is at least in good health and can devote his energy to the tasks allotted him The victim of an arthritis is not only incapacitated to a comparable degree, but is additionally suffering pain and discomfort Carefully considered efforts at the prevention of this disease would have large justification

As mentioned earlier, the purposes of this study included making overseas, at the site where most cases developed, adequate provision for meeting this problem along lines most clearly indicated Any such plan would have called for centers for the segregation and treatment of these patients and a base or bases where the more refractory types could receive detailed and thorough care In addition, there has been indicated the necessity in this country for analogous distribution and care of these subjects, including those returned from overseas

Fundamental to successful treatment of this large group of men is adequate provision of medical personnel and physical facilities in the way of at least the simpler forms of baking, hydrotherapy, etc It is not to be expected that at subsidiary centers much could be developed

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20 Through the courtesy of Col A G Love of the Sick and Wounded Division, Office of the Surgeon-General, Washington, D C, data have been obtained, based on the year 1918, which show an incidence of about 35,000 cases for an army of 4,000,000 men for one year

It is to be borne in mind that in only about five months of this year were United States forces engaged in active warfare on a large scale Furthermore these figures are for primary arthritis only and not for rheumatic fever or arthritis complicating any other disease, although it is clear from the present studies that many, if not all, cases of rheumatic fever also belong in this category In view of these considerations it seems fair to postulate an incidence of 40,000 or more cases of all types for an army of 4,000,000 men for one year

along these lines but it should be possible in any base hospital to which these men are first admitted, to discover and remove obvious focal infection. The failure to do so was an omission frequently illustrated in the present series. The prompt recovery of certain soldiers, who had been invalided for variable periods of several months or more, on the removal of easily demonstrable foci, proved beyond doubt that many patients presenting foci on admission had been neglected. It was clear that considerable attention had been paid to foci as etiologic factors, but appreciation of their rôle does not necessarily afford the experience requisite to discover and remove them, nor can the best intentioned and most skilful medical officers care for more than a limited number of patients. It was obviously due, in part, to this fact, that under the stress of warfare many patients suffered unduly. The evidence obtained from the histories of many of these men, however, makes it plain that no systematic and regular policy was followed in regard to them and that such cases were probably not unfrequently regarded as of secondary importance or too refractory to warrant much emphasis.

It is quite clear, therefore, that were the war still in progress something real could be achieved by emphasizing and systematizing the treatment to be given these men on their admission to the first hospitals that could properly undertake such work.

The problem of the personnel and equipment to be provided at the bases is an important one. The results of this study suggest that it would have had to be met on a large scale. Sufficient space has been given to the various forms of treatment to indicate that the external forms of therapy, which in civil life so frequently meet with disappointing results, must be accorded greater value when considering this group. It is believed that this point should be emphasized as a practical measure of large importance to the conditions under discussion. It is possible that such saving of effort could be achieved, as was apparently attempted, by establishing such bases at existing water resorts, but this consideration alone should not be allowed to dominate. In a disease in which improvement or cure sometimes depends on the coordination of a number of factors, each of limited value alone, advantage should be taken of every condition known to have favorable influence. Among such conditions is the question of climate. Students of arthritis would probably agree that a damp enervating climate is undesirable and that low valleys and the sea coast should be avoided as sites for treatment. The present observations at U. S. Army General Hospital No. 9, were carried on in the midst of a thick pine belt on a sandy soil which quickly absorbed moisture, but there was no altitude and the sea was only nine miles away. Our experience has

shown that although the dampness and the abrupt changes of temperature were much modified, climatic conditions were not ideal. It is quite clearly indicated that the most desirable site for the establishment of a treatment center for arthritis is inland, in a dry region of fairly equable climate, with reasonable altitude of, say, 600 feet, a greater altitude would be advantageous.

Coordination of the many agents which have application to arthritis, rather than dependence on one or two measures, constitutes a desideratum emphasized by this study. In few centers for treatment is this attempted to an important degree because most of them are dependent upon and due to the partial success of measures developed locally.

Success in coordination depends on competent direction, in the first place, and on the caliber of those conducting the various accessory activities drawn on, in the second place. Perhaps no other disease demands more in this connection. Experience in civil life and with more than 400 cases in this series has shown that this latter conclusion is particularly true of the specialties of the nose and throat, and of dentistry. The recognition of causative foci in the throat and head requires the widest possible experience.

Treatment of the sequels of arthritis has so often necessitated painstaking and patient efforts on the part of orthopedists, that the burden of care for all parts of this important field in civil life has fallen on them more frequently than on internists, with the result that some of the most important contributions to pathology and treatment have originated with orthopedists. The problem of arthritis, however, is fundamentally medical, and it should be necessary to call on orthopedists only to differentiate doubtful conditions, and to care for the sequels of long standing processes. The importance of orthopedic cooperation must not be overlooked, however, in considering this subject from the purely medical viewpoint. The many cases analyzed during the present study have served to indicate that it would be impossible to give adequate care to arthritic soldiers under warfare conditions without assistance from experienced orthopedists. For example, the attempt has been made under the caption "clinical considerations" to emphasize the difficulties of differential diagnosis in certain types of cases, particularly those with disabilities referred to the back. The field included here is very large and it is easy for the internist to overlook pathology of an orthopedic nature and to make incorrect diagnoses. The roentgen ray is of very limited assistance in these relatively early cases, and the factors actually producing sciatic pain, sacroiliac, paravertebral and even vertebral pain are often difficult of analysis. In addition to the necessary cooperation just indicated, it is obvious that adequate orthopedic assistance is essential for cases needing immobilization, extension, braces and the like.

Provision for the routine examination and ward care of arthritics is not as simple as may appear. These steps must precede all others and determine the lines of treatment finally followed. It is difficult or impossible for the chief of a large arthritic service to keep before him the detailed needs of such cases, although many of them call for long experience in their proper classification and disposition. Such action must fall in general on younger and less experienced men. No systematized plan of treatment of arthritis has been evolved to date, and results from any and all measures have so frequently been disappointing as to produce confusion and a general attitude of indifference or even hopelessness among all concerned. On the other hand, the topic of arthritis enters a variety of different and opposite domains of medicine and surgery, some of which are apt to believe that they hold the key to its solution. Clinical manifestations of the disease generally concern structures primarily within the field of orthopedics, and interest on the part of medical men in the underlying pathology is often wanting. As just mentioned, however, the disease is properly comprehended by internal medicine and the final solution of its etiology, prevention and treatment must be sought for in clinical and laboratory investigation, proceeding from this premise. Notwithstanding the omnipresence of this disease it seems that physicians are too rarely accustomed to interpret critically the symptoms of these patients, to classify the types encountered, and to employ the desired discretion in the forms of treatment adopted. Apart from the shortage of well trained medical men in the army hospitals at large, it is probable that a difficulty in making adequate provision for the treatment of arthritis on the large scale which continuation of the war would have necessitated, would lie in obtaining medical officers whose previous interest in this field would find added stimulus in the large opportunity presenting. Without an interest below the surface, the routine care of arthritics soon becomes monotonous to the detriment of the patient. The problem of the arthritic is largely individual, in this it is somewhat comparable to the problem presented by the various forms of neurasthenia which the war has produced in such large numbers, and cannot as yet be met by wholesale measures alone.

#### CONCLUSIONS

1 Chronic arthritis is one of the larger medical problems affecting the soldier in service. Soldiers developing it have had previous attacks with a frequency about five times greater than have soldiers admitted to hospital for other conditions at large.

2 Exposure was the exciting factor in 58 per cent of 400 cases studied. Critical examination of all patients revealed apparent foci of infection in 72 per cent. Although the etiologic importance of focal

infection, especially in civil life, is not to be minimized, it is clear that the present group showed a considerable independence of it. One hundred and eighty-four patients, or 46 per cent, recovered in the presence of demonstrable surgical foci. This is nearly three times the number which improved (sixty-five cases, or 16.25 per cent) after the removal of foci. The tonsils were most frequently the site of infection (52 per cent), the teeth were next (33.5 per cent), the genito-urinary tract came last (12.5 per cent) and clearly played an almost negligible rôle in causing arthritis.

3 The sites of most frequent involvement were the knees (62 per cent), the ankle (35.25 per cent), the hip (33.75 per cent) and the shoulder (31.25 per cent). All things considered, however, it is not clear that trauma to weight bearing parts, caused by hiking, drilling, etc., played a much greater rôle than it does in civil life in determining the site involved.

4 The basal metabolism was found to be normal in 80 per cent of twenty-nine cases studied. In 20 per cent it was slightly below normal limits.

5 The carbon dioxide combining power of the blood, the total fat, the cholesterol and the calcium of the fasting blood were found to fall within the accepted normal limits.

6 About one half of forty cases of arthritis studied showed an abnormally high value for blood creatin. Certain of these showed a decline in blood creatin coincident with clinical improvement.

7 The urea of the fasting blood in seventeen cases fell within normal limits. The nitrogen of the fasting blood in sixty-seven observations in fifty-seven cases fell within normal limits, with two exceptions.

8 Studies of the renal function, in thirty cases of arthritis of widely different types, by means of the so-called nephritic test meal, gave results which fell within the accepted ranges for normals. When compared with nine normals under similar conditions there is evident a slight lag in the elimination of water, nitrogen and particularly of salt. In conjunction with the normal blood nitrogen and urea values mentioned in the last paragraph, it seems fair to conclude that there is no marked dislocation of renal function in chronic arthritis, though this function may be slightly lowered in some cases.

9 In studies on arthritics representing all degrees and stages of the disease it was found that there is a lowered sugar tolerance in a large proportion of cases. This lowered tolerance accompanies the great majority of severe cases and is roughly proportional to the activity of the arthritic process per se. It returns or tends to return to normal with convalescence or recovery.

10 The return to normal is apparently independent of the type of therapy employed, but is most abrupt after the removal of causative

foci of infection In certain severe chronic cases from which all demonstrable foci have been removed, a lowered sugar tolerance seems to persist

11 Apparent foci of infection, unproductive of systemic effects, are not necessarily accompanied by a lowered sugar tolerance A lowered sugar tolerance from focal infection apparently accompanies the failure of the organism successfully to maintain its wall of defense In this light a lowered tolerance becomes an intermediary step in the pathology of arthritis and possibly other conditions as well

12 A lowered sugar tolerance seems to stand in relation to many infectious or inflammatory conditions at large, and to depend on more fundamental pathologic processes than has been appreciated It is also of more common occurrence than has been recognized

13 The lowered tolerance observed in some diseases and referred to them may sometimes have been due to focal infection rather than to the diseases under consideration It is important that foci of infection be eliminated from consideration when miscellaneous conditions are studied in this regard

14 Critical examinations of recruits for a history of previous attacks of arthritis would reveal cases most likely to develop it It is reasonable to believe that rejection of this group or at least the worst cases in it would importantly reduce the incidence of arthritis in the army A more conservative policy would segregate such cases, examine them for foci of infection and remove such foci when found This would have the added importance of prophylaxis towards the civil community These measures could be combined by applying one or the other appropriately

15 The several forms of therapy here discussed have all application to the group under consideration Treatment of large numbers of cases, however, requires methods capable of wide routine use Local and external measures in the sense indicated have unexpectedly large application because of the tendency of this group to improve under favorable conditions, they are also susceptible of easy routine employment

It seems that in some cases of arthritis in this series six months or a year were needlessly lost Earlier and more critical attention to focal infection, as a basis, together with a large coincident use of local measures, would probably afford the routine therapy best adapted to reach the greatest number of cases and should importantly curtail the existing invalidism Many patients would require more individual attention, however, such as treatment by nonspecific protein injection or a restricted diet

16 Experience with treatment by a restricted diet, as here described, corroborates in the present group, the conclusions previously published regarding it. Such therapy finds additional support in the studies on blood sugar, revealing a difficulty in the utilization of carbohydrate. It seems clear that success following this measure depends on catering to a weakened function of which the lowered sugar tolerance is one evidence. Treatment along this line has undoubted application in appropriate cases of chronic arthritis.

17 The several measures of value in arthritis should be combined in their application to the present group more frequently than obtains in the treatment of cases in civil life. The tendency to focus on one measure often results in failure where the subsequent coincident use of several measures results in benefit.

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#### CLINICAL ABSTRACT OF CASES

The large numbers refer to the hospital register number. This list includes nearly all cases which were the subject of laboratory investigation. A few other cases are mentioned in the text, but not included here, as the data accompanying them are sufficiently full for the purposes intended. The hospital register number is missing in a few cases owing to the inaccessibility of records following closure of the hospital.

CASE 1 (No 2656)—Lieut Robbins, aged 25. One previous attack of rheumatism nine years before, lasting three months. After two months of pain in right shoulder attributed to bayonet drill, he was taken sick in September, 1918, with swelling and pain in the left ankle for which he went to the hospital. Involvement of other joints was progressive, finally affecting the right shoulder, right foot, knees, hips and scattered muscle groups. On admission to U S Army General Hospital No 9 he had had one tooth extracted for an



apical abscess about eight weeks previously, without benefit. There was apparently no other focus of infection, the tonsils being repeatedly pronounced normal. This officer made a complete recovery by dietary measures alone, improvement dating abruptly from their institution. Details are given under "Dietary Considerations."

CASE 2—Karl Haeberle, aged 26, white. No previous attack. While drilling on rough ground May 2, 1918, the right ankle became swollen and painful. This case ran a long chronic course suggestive of tuberculosis. He failed to improve following tonsillectomy, one month after onset, with attention to abscessed teeth. There was much edema, elevation and rest proved of no avail. The final diagnosis of an unusual type of bone atrophy following trauma was made by Colonel Brackett, division of orthopedic surgery, Surgeon-General's Office, and under his advice the patient was given exercise. The foot then improved and on closure of the hospital in June, 1919, he was well on his way to recovery. He was again seen in November, 1919, and had made further marked improvement, the foot appearing nearly normal.

CASE 3 (No 2485)—Blowers, aged 24, white, infantry. December, 1917, he sprained the left ankle. While in the hospital for treatment, he developed rheumatism in the legs extending to the right knee, hand, elbows and fingers. He made a fair recovery within several months, but about six weeks later he was again taken sick. There were no demonstrable foci of infection and on discharge, about January, 1919, the patient had made recovery to the point where his disabilities were muscular, with occasional stiffness and pain on climbing stairs, which condition remained about stationary.

CASE 4—John McGrann, aged 44, white. Following gunshot wound of back was taken sick in July, 1918, during convalescence, with pain and weakness in the muscles of the back and spine. The roentgen ray showed arthritis of the spine. No foci of infection were detected, except, possibly, in the gums, which were in rather poor condition, and in pockets about the teeth. These received attention and he made a slow and limited improvement of about 60 per cent, being discharged about April, 1919.

CASE 5 (No 2583)—Beck, aged 26, white. Previous attack of multiple arthritis three years before, which followed three months after a gonococcal infection. He was accepted for full duty, and at the end of September, 1917, following a cold, he was affected by swelling and pain in the knees and ankles, but improved enough to embark for France, but was again taken sick on ship board with extension of the rheumatism to the right shoulder and the hands, since when he did no duty. This patient made a limited improvement following tonsillectomy, August, 1918. Attention to his teeth in November, 1918, was of further value, and he was apparently well when discharged, Jan 2, 1919.

CASE 6—William Hayes, sergeant, aged 29, white. In 1916, he suddenly developed arthritis of the left foot and wrists extending to the fingers and knees. Under treatment at Hot Springs the foot recovered, but after some improvement in other joints he again grew worse, the right wrist becoming ankylosed. Tonsillectomy in December, 1918, and attention to the teeth were without benefit. This patient made an abrupt 50 per cent improvement under dietary measures to which were later added potassium iodid, cod liver oil and daily sweats. He left the hospital symptomatically well in May, 1919. This case is described in full under dietary considerations and was very instructive throughout, illustrating what can be achieved in the most severe types by combinations of treatment, if the basis for convalescence be established.

CASE 7—Ben Jaffy, aged 24, white. Previous attack of arthritis of right knee in 1913, confining him to bed for four months. The present illness began in the right shoulder in July, 1918, following exposure. A tonsillectomy had been performed in 1913. On admission the knees and shoulders were markedly involved, and he presented focal infection in one abscessed tooth, which was extracted December 20. He made a rather abrupt improvement following

this, and then remained in statu quo for a number of months. Improvement did take place, however, and in May, 1919, he was discharged having made about 75 per cent recovery and was still improving.

CASE 8—Albert Martin, aged 44, white, was taken sick in March, 1918, with arthritis of the right ankle and knee extending to the hip. He became bed-ridden, and his case ran a protracted course without the slightest improvement. There were foci in the tonsils, which were removed Dec 30, 1918, without benefit. There was evidence of renal calculus, and the liver was enlarged four finger breadths. The physical and mental condition of the patient were not suited to radical therapy or that requiring his cooperation. This case was one of the most advanced and refractory in the entire series.

CASE 9—Enrique Beeman, aged 24, white, gave a history of previous disability in the hips and sciatic region. The present illness began acutely in February, 1918, following drilling and exposure, and affected the left hip, right ankle and the back muscles. He made an essential recovery, but because of residual symptoms, tonsillectomy was performed Dec 2, 1918. Six weeks later, this had apparently had no influence, and he was discharged complaining of shifting and intermittent disability in muscles of back and legs.

CASE 10—Naseeb Masood, aged 23, white, had had no previous attacks. In April, 1918, he was gassed and underwent exposure in the trenches, following which there developed arthritis in the hips, knees, ankles and back. Since this date he walked only with crutches, remaining a bed-ridden patient until discharged from the hospital. There was definitely no dental focus, genito-urinary examination was negative and his tonsils were removed Nov 15, 1918. This was without the least effect, and his condition was the same on discharge, March 2, 1919. This case was of much interest in that the patient's disability consisted in exquisite tenderness on active or passive motion of the knees or on palpation. There was also exquisite tenderness at the metatarsophalangeal articulations of the feet. The roentgen-ray findings were negative and a marked psychic element was suspected, but he gave repeatedly a greatly lowered sugar tolerance, and it seems proper to regard this case as one of marked severity of the fibrous type, giving little or no contracture or roentgen-ray changes and running a protracted and obstinate course.

CASE 11—George Hinman, aged 25, white, was taken sick gradually following exposure, February, 1918. After improving, he was again taken sick with arthritis involving the knees in August, 1918. His chief symptom during observation consisted of slight disability of the right knee and intermittent sharp exacerbations of arthritis in one or the other wrist, accompanied by redness and swelling, the roentgen-ray findings were positive, all foci were reported negative. This patient made a modified improvement under a slightly lowered fixed intake of food, but the results were not sufficient to warrant a detailed report, as he developed acute tonsillitis following which tonsillectomy was performed April 2, 1919. The tonsils were found to be diseased and the patient thought he felt a definite improvement following their enucleation.

CASE 12 (No 2662)—Thomas Boyd, aged 24, white, began to have attacks of rheumatism nine years before, being in bed frequently for from four to six weeks. He had had no attacks for the last three years, but had had three or four attacks of tonsillitis. He did full front-line duty in the trenches. While drilling in rest camp in April, 1918, he began to have pain in the muscles of the legs and later in the back, often accompanied by febrile exacerbations. Tonsillectomy was performed Nov 4, 1918. He had no dental or genito-urinary foci but was definitely not cured by this procedure when discharged March 10, 1919.

CASE 13—Mrs Lum, aged 42, white. This woman had had arthritis for nine years, with deforming arthritis of the hands and wrists and was studied by permission of the commanding officer. She had had exhaustive attention given to all foci without avail, and her tonsils were repeatedly pronounced so small

as to be almost absent. Among operative procedures to remove foci were appendectomy and cholecystotomy, but the gallbladder was normal. Tonsillectomy was performed in June, 1919, as a routine procedure. Culture was negative for hemolytic streptococci and she was no better in February, 1920.

CASE 14 (No. 3559)—Lowe, sergeant, aged 42, white. In 1916 he had rheumatism in the ankles, knees and wrists, bilateral, with a severe attack in June, 1917, but he recovered from this. October, 1917, the present attack began. His tonsils were removed about July, 1918, without any improvement, and he had no other foci. This case was one of great interest and was apparently an extreme example of the fibrous type, accompanied by few or no external evidences and only slight changes shown by the roentgen ray along the shafts of the phalanges of the hand. An osteophyte was removed from one heel in 1917. He was subjected to no less than thirteen different kinds of treatment, including baking, sweats, nonspecific injections, etc. He thinks the protein injections made him worse. There was not a little analogy between this case and Case 10 (Masood) which was not, however, so far advanced. Because of a small nasal polyp, operation was directed toward its removal and treatment of the ethmoid air cells, but without obvious results. This patient was exquisitely tender wherever touched on his hands, knees and feet and although able to move slowly, he was essentially chair-ridden. His mental outlook was excellent, and there was no psychic element. The failure of benefit under a short period of restricted diet is described under dietary considerations. He gave a number of different interesting laboratory findings.

CASE 15—Arthur Studebaker, aged 23, white. This soldier was big and well built. He contracted measles at Camp Sherman, May 23, 1918. After nearly three weeks in the hospital, he was discharged, but got wet sleeping in a tent and was taken sick with swelling of the right knee and the ankles, and the left hip, with fever and pain. After much improvement under salicylates, a tonsillectomy was performed about July 1, 1918. An apical tooth infection was removed, but without hastening the rather slow recovery. The right knee remained painful, and the knee was put in a cast for three weeks, after which another cast was applied for three weeks again. He thinks this made him worse, as also did hot fomentation, rubbing and baking. On admission to U. S. Army General Hospital No. 9, Jan. 9, 1919, his knee was exquisitely tender to touch, with limited function but no deformity or visible objective evidences. Tenderness apparently followed the synovial membrane extending up over the area of the joint capsule. It is possible that this soldier still presented a small dental focus on his discharge, in the condition described, about Feb. 1, 1919. His case was apparently identical in nature with Cases 10 (Masood) and 14 (Lowe).

CASE 16—Br., aged 45, white, civilian. He had had for nearly fifteen years a progressive arthritis, characterized chiefly by intermittent incapacitating exacerbations with sciatic pain and malaise in the interim. This case had been exhaustively searched and treated for twenty-four months on the basis of focal infection. The tonsils were removed, the genito-urinary tract was given much attention and all dental factors were cared for. All these activities availed only to induce a slight improvement, and the severe exacerbations continued. Under a restricted diet this patient made an abrupt and gratifying convalescence, amounting to a 90 per cent cure, and again resumed his full legal practice with greater energy than he had felt for fifteen years. Observation of this case for about three years reveals that this improvement is maintained and unmistakable. The facts of this case admit of no ambiguity. The greatly lowered sugar tolerance obtained, illustrates apparently, together with other cases, that the lowered tolerance may persist in the absence of or after the removal of all demonstrable surgical infection. He was studied by permission of the commanding officer.

CASE 17 (No 2976) —Faulkner aged 20, white In January, 1918, several weeks after an injury to the left ankle, he developed pain and swelling in the ankle, knees and right hand and finally nearly all joints were involved Tonsillectomy was performed Jan 9 1919, although at that time he had made a very substantial improvement which seemed to relate chiefly to the change of climate in coming from Camp Shelby The tonsils were found diseased

CASE 18—Samuel Muse, aged 23, colored This soldier presented widespread tuberculosis of the periosteum and bones of the arm and phalanges of the hands, together with involvement of some of the soft tissues of the arms The diagnosis was long in doubt, there were exposed and denuded areas of bone, and there was presumably secondary infection This case was studied as an example of miscellaneous disease The case is reported here because of the laboratory observations

CASE 19 (No 3609) —Fouts, aged 27, white He had had severe rheumatism of the right leg, thigh and back when 5 years of age June 9, 1918 there developed, during drilling disability in the back right thigh and leg without joint swelling but with stiffness This man presented on admission, the symptoms of acute myositis of the muscles of the right leg with exquisite tenderness to pressure Two teeth were abscessed, but there were no other foci and roentgen-ray examination of the extremities was negative After critical study this soldier was found to have forward dislocation of the fifth lumbar vertebra, apparently originating from trauma

CASE 20 (No 3658) —Wasson, aged 21, white had had no previous attack of rheumatism and did full duty until August, 1917, when he fell, hurting his right hip After two or three days he again did full duty Six weeks later the right hip became painful and a cast was applied After removal both knees became swollen and the elbows and fingers of the right hand and wrist became stiff, the right ankle was sore but not swollen The full differential blood counts were normal, but there were changes in the shape and size of the red blood corpuscles The platelets were decreased This soldier was apparently entirely free from demonstrable surgical infection On admission to U S Army General Hospital No 9 the symptoms in the hands and wrist were intermittent and slight, but the hip necessitated a cast and orthopedic treatment in bed He was still in bed in May, 1919

CASE 21 (No 3645) —Whittington, private aged 29, white, had had no previous attacks He did full infantry duty until December, 1917, when he stood in water up to his knees while fighting a fire in France From this date he had disability progressively in his ankles, knees, hips, shoulders, elbows, wrists and fingers of both hands with fever After six or seven months in bed, he improved considerably and on admission to the hospital the chief evidences were in the left knee which was kept flexed There were diffuse symptoms of varying intensity in the hands and elsewhere, but vertebral arthritis was apparently the most active cause of trouble This patient had dental, tonsillar and genito-urinary foci when he was taken sick, and their removal was apparently of benefit, although he was still considerably disabled about May 1919 The greatest relief was obtained from an orthopedic brace

CASE 22 (No 3712) —Oberger, aged 24, white had six previous attacks, beginning in early childhood He did full duty in the medical corps and after some stiffness in the hips in the spring and early summer of 1918, he was taken sick Aug 23, 1918, in France, with exacerbation of previous disability and fever He was confined to bed, and the trouble spread to the left shoulder and later, after the application of a cast from the waist to the hips, it spread to knees This case was very severe from the start, and was treated overseas by foreign protein injections which caused severe reaction and increased local tenderness He also received baking, massage, electricity and other treatments Examinations at other hospitals had revealed no foci On admission this patient presented hypophotic ankylosis of the entire spine, great disability

with marked roentgen-ray changes in the left shoulder, complete ankylosis of the hips and practically also of the knees. Shortly after admission an abscessed root was removed with apparent benefit. This patient was treated with interesting and beneficial results by reduced diet. The case is fully described under "Dietary Considerations." He was the subject of many laboratory studies. On his discharge about May 25, 1919, he was greatly improved, could walk on crutches, and had full rotation and increased flexion of the hips and considerable flexion of the knees. The spine apparently presented a bony ankylosis. Two weeks before discharge, after his improvement had become established his tonsils were removed as a prophylactic measure. They were found very small and necrotic, and showed *Streptococcus hemolyticus*. This soldier was not making important progress before treatment was undertaken, and the result in this case was not open to question. Further interesting features are described under "Clinical Considerations." He reported himself as doing very well in August, 1919.

CASE 23,—C O'Brien, aged 32, white, orthopedic service, was suddenly affected May 30, 1918, following exposure, with pain, swelling and redness of the right knee and ankle. Foci were reported as negative on admission. Roentgen-ray examination showed bony destruction, spur formation and atrophy. The diagnosis in this case was complicated by the possibility of gonococcal or syphilitic infection and occasional exacerbations due to trauma when drunk. The knee was greatly enlarged, hard, painful on motion, which was limited, but was not very tender on palpation. Rest in a cast achieved much subsidence and some return of function.

CASE 24—Miss S, army nurse corps, aged 48, white, was taken sick in August, 1919, while at Camp Meade, with pains in the hips and the calves of the legs. The nature of her condition was in doubt, but finally it was diagnosed as myositis of a rheumatic nature for which she was referred to U S Army General Hospital No 9. No foci of infection could be detected. There were trifling, almost microscopic overgrowths on the shafts of the phalanges to which only doubtful importance could be attached and the diagnosis of rheumatism or arthritis could not be established. She presented scattered tender points in the legs and gluteal regions and incision over one tibia showed numerous fatty accumulations which were negative on examination and to culture. The sharp contrast of her pain and the normal sugar tolerance first suggested the nonrheumatic nature of this case.

CASE 25 (No 3674)—Eckman, private, aged 29, white. This case was studied as an example of a convalescent arthritic. He had rheumatism in September, 1917, and was in bed for three weeks. Sept 26, 1918, after exposure, he was acutely affected by swelling, and tenderness of the knees, ankles and calves. Nine teeth were extracted at this time. He began to improve in November, 1918, and was entirely well when discharged Feb 10, 1919. He had been in bed for ten weeks. On date of sugar tolerance test patient had been well for about eleven weeks. Apparently he had no foci of infection on this date.

CASE 26 (No 3807)—Mosely, private, aged 29, white. This man was studied and reported as a case of convalescent arthritis. He had had no previous attacks of rheumatism. He was taken sick May 14, 1918, following exposure, with pain in the knees, hips, leg and thigh muscles, without swelling. There were foci in the tonsils but he made a recovery without their removal and was entirely well when discharged Feb 10, 1919. He had been in bed for three weeks and in the hospital for six weeks.

CASE 27 (No 3196)—Sephers Black, private, aged 26, white, had had inflammatory rheumatism at 8 years of age. The present illness began October, 1918, about two weeks after a severe pneumonia with rheumatic pains in the left leg, then the left shoulder and arm, then both arms and legs. The late

onset after infection is to be noted. He had been practically free from symptoms for five weeks on the date of sugar tolerance test, Feb 10, 1919. There were foci in the tonsils on this date, and he recovered in spite of them.

CASE 28 (No 3329) —Fred Stone, sergeant, aged 40, white, had no previous attacks. Following exposure, in February, 1918, he developed arthritis of the spine, shoulders and hips. He had had dysentery in June and August, 1918. His rheumatism did not prevent his continuing on duty in a machine-gun battalion, but about September, 1918, he went to the hospital and never returned to duty. Several teeth were extracted in October because of abscesses and he made a substantial recovery. On the date of the sugar tolerance test, February, 1919, his symptoms had been absent for three weeks.

CASE 29 —C Collins, aged 27, white, had had since his twentieth year from one to three attacks of rheumatism yearly, involving the knees, hips, shoulders and ankles, without swelling. Present illness began Nov 9, 1918, following dysentery, and affected the hips, shoulders and knees. He was in bed five weeks, two months prior to the sugar tolerance test made Feb 10, 1919. Freedom from symptoms had then lasted five weeks. Apparently no foci were present on this date.

CASE 30 (No 3716) —R Stewart, aged 26, white, had no previous attacks. September, 1918, following dysentery, there developed gradual swelling and pain of the left knee. He had had abscessed teeth which were not removed, but he made a complete recovery. At the time of the sugar tolerance test, Feb 11, 1919, he had been well for seven weeks.

CASE 31 —Moehler, aged 34, white, had no previous attacks. Present attack began gradually in October, 1918, and involved the back, hips, thighs, knees and ankles, with swelling. All foci were reported negative and he was well on the date of sugar tolerance test, Feb 11, 1919.

CASE 32 (No 3919) —Moon, aged 31, white, had a suggestion of rheumatism in the legs in 1914 and in October, 1918, while in the hospital with diarrhea he was affected with pain and swelling in the knees and ankles. There were apparently no surgical foci, and he had made an entire recovery at time of sugar tolerance test, Feb 11, 1919.

CASE 33 —G Cullen, aged 30, white, had no previous attacks. Present attack began gradually, following exposure June, 1918, affecting the right hip, then the left hip, left leg and the shoulders. The teeth showed foci. He took salicylates in large doses overseas, but the condition ran a slow course. He had been practically well for seven weeks when the sugar tolerance test was taken, Feb 12, 1919. He then had a possible focus in one tooth. No foci were removed in this case and the tonsils had been enucleated twenty-one years before.

CASE 34 (No 3676) —Gaffney, aged 19, white, had a slight attack of rheumatism in 1915 with "sore joints." The present attack began June 15, 1918, involving the thighs and knees with swelling. He kept with his company until September when he had to go to the hospital and he never returned to duty. There were no demonstrable foci in this case. He was taken sick five months before, and had been well for three weeks prior to the sugar tolerance test, made Feb 12, 1919.

CASE 35 (No 3625) —Cabbage, aged 27, white, had no previous attacks. In June, 1919, following exposure, there gradually developed disability in the lumbar spine and the right knee. He made an essential recovery in the presence of foci in the tonsils, which were removed on the day following the sugar tolerance test made Feb 12, 1919.

CASE 36 (No 3201) —Clement sergeant, aged 29, white, had no previous attacks. September, 1918, following dysentery, there gradually developed tenderness and swelling of the knees, feet, ankles and finally all the joints. He made a recovery in the presence of dental foci which were still present on the date of sugar tolerance test, Feb 17, 1919. At this time his residual symptoms

were chiefly tenderness and pain in the heels on pressure and motion, with some swelling. March 17, 1919, he was practically well and afforded one of the few instances of practically convalescent arthritics still retaining a high sugar curve.

CASE 37 (No 4037) —Chester Tally, aged 19, white, had no previous attacks. Oct 27, 1918, following exposure, rheumatism began in the right knee, leg and foot, with slight swelling. He went to the hospital and never returned to duty. He recovered in the presence of an abscessed tooth which was not removed and on the date of the sugar tolerance test, Feb 19, 1919, he had been well for two months. At this time he also had hypertrophied tonsils, which the eye, ear, nose and throat department reported, however, to be free from foci of infection.

CASE 38 (No 4027) —Morris, private, aged 23, white, had no previous attacks. Sept 27, 1918, he developed pneumonia and was in bed until November 14. Six days after leaving bed his ankles became swollen and painful, followed by disability in the knees, thighs and hips. There were foci in the tonsils, but tonsillectomy was refused as he had recovered by Feb 19, 1919, the day of the sugar tolerance test. Operation was not insisted on. On this date his freedom from trouble had lasted about three weeks.

CASE 39 (No 4047) —Albert Thompson, aged 25, white, had occasional pains in his feet during the past four years, but no clear rheumatism. About September 21, he developed rheumatism in the right knee which became swollen and painful, he then spent six weeks in the hospital and never returned to duty. There were foci in the tonsils, which were removed after the normal sugar tolerance test on Feb 19, 1919, on which occasion the right knee had nearly full function and was not tender, but possibly was still slightly enlarged. His state of improvement had then lasted about one month.

CASE 40 (No 4021) —Gross, aged 24, white, had no previous attacks. In September, 1918, he developed pneumonia in France and was in bed three weeks. After recovery, he returned to his work as truck driver. He developed rheumatism early in November in the right ankle, it then spread to the left ankle and knees, which became swollen. He was exposed to cold and wet at the time of onset. He kept at work for two weeks and was then sent to the hospital and was in bed for three weeks. He never returned to duty. This patient had chronic tonsillitis, and on the date of a normal sugar tolerance test, Feb 20, 1919, he was practically well, three and a half months after onset. His present improvement had lasted one month. No foci were removed.

CASE 41 (No 4184) —Greenberg, private, aged 26, white, had no previous attacks. The onset of his condition, Oct 20, 1918, followed exposure, and began with pain in the hips and knees. There were apparently no demonstrable surgical foci of infection in the teeth or in the genito-urinary tract, the tonsils were cryptic. He had been well for six weeks by the date of practically normal sugar tolerance test, Feb 20, 1919.

CASE 42 (No 4001) —Kerr, aged 22, white, had rheumatism in the knees and ankles when 6 years of age. In October, 1918, he had influenza, after recovery he was sent to a replacement camp and did eighteen days of full duty. He was taken sick in December with rheumatism of the knees and ankles. There was a chronic tonsillitis without symptoms, but he made a complete recovery. On the day of the normal sugar curve, Feb 20, 1919, he had been well for one month.

CASE 43 (No 4194) —Wilburt, aged 40, white, had no previous attacks. Present illness began October, 1918, following exposure, with stiffness, but no swelling, involving the elbows, knees, wrists, ankles and last the feet and fingers. On admission symptoms were confined to the fingers, elbows and knees, and on the date of a very slightly elevated sugar curve, Feb 21, 1919, he was nearly well. His tonsils were removed subsequently and were negative for *Streptococcus hemolyticus*. This relieved trifling residual symptoms.

CASE 44 (No 4187) — Brake, corporal, aged 20, white, had no previous attacks Oct 24, 1918, he developed dysentery which lasted three or four days While in the hospital, and one week after the attack of dysentery was over he developed rheumatism of the metatarsophalangeal joints of the feet The tonsils were positive for foci, and he had made a considerable improvement on admission Tonsillectomy, March 27, possibly benefited him slightly, but more improvement followed nonspecific protein injections On the date of a normal sugar tolerance test, Feb 21, 1919, he presented a tonsillar focus and distinct, but mild, symptoms which had improved and were still improving The tonsils proved to be diseased slightly

CASE 45 (No 4295) — Barger, aged 22, white, had one previous attack in the spring of 1916 He did full duty in the infantry overseas August 30, pains began in the left knee, hip, ankle, elbow and right shoulder He remained with his company until October 29, when a rectal abscess developed An operation was followed by recovery in four weeks Rheumatic pain continued while he was in the hospital, but became worse after the operation He never returned to duty but made a slow improvement In January, 1919, he had an attack of measles in this country with sharp recurrence of arthritis On admission he presented an intense arthritis of the left hip and the metatarsophalangeal joints of the left foot, the knee being kept flexed in bad position and immovable This case was of great interest and is described under "Studies on the Blood Sugar" He gave a high curve when seen Feb 27, 1919, and about one month later, when entirely well, two weeks after tonsillectomy, he gave a normal sugar curve It is important to note the apparently contributory role of the tonsils and the delay of more than six months of invalidism before their removal

CASE 46 — Hetherington, aged 40, white, had no previous attacks Present illness began August, 1918, after being gassed and injured in the back The chief symptom was spondylitis, with changes demonstrable by the roentgen rays There were foci in the teeth and tonsils His condition was stationary until after extraction of six teeth, when improvement became marked He gave a high sugar curve March 6, 1919, and a nearly normal curve six weeks later when the teeth had been extracted

CASE 47 (No 4049) — Chaney, aged 29, white, had no clear rheumatism but some knee trouble in 1916 He did full duty carrying a machine-gun tripod, which he thinks induced him to stoop and started the pain and stiffness in the spine and back muscles during August, 1918 In October he developed influenza and was in bed three weeks which was followed by aggravation of his rheumatism A slow improvement resulted and on admission he was stoop-shouldered and apparently fixed in that position This case was of much interest and was thought to be tuberculous, but the intercurrent of other rheumatic symptoms in the left knee, hip and shoulder proved its rheumatic nature He gave a negative reaction to tuberculin The tonsils were diseased They were removed with no apparent benefit Roentgen-ray examination was apparently positive The lumbar spine was flattened and fixed and there was marked kyphosis in the upper dorsal region At the time a slightly elevated sugar curve was noted, March 6, 1919 his tonsils had not yet been removed and he was in an interim between exacerbations

CASE 48 (No 4238) — Jansen, aged 32, white, had an attack five years before involving the ankles, knees and hips Present attack began gradually, about May, 1918, involving the back, knees, hips and ankles Confinement to bed in a sitting position apparently induced a stooping posture which required him to support his body above the waist by placing his hands above his knees The tonsils had been removed in January, 1919 After admission in February, 1919, after long observation, the patient was found to be improving slowly but steadily, assisted by external measures A psychic element was suspected but



he gave in the absence of foci an elevated sugar curve. Roentgen-ray examination was negative, but this was probably a true instance of arthritis. This case and the preceding one emphasized the desirability of orthopedic assistance and the difficulty in reaching a correct diagnosis. See "Clinical Considerations."

CASE 49—Kotschorek, aged 25, white, had no previous attacks. Present attack began Oct 1, 1918, following injury, with involvement of the lumbar spine, left hip and right knee. This case was on the orthopedic service and proved to be apparently tuberculous. He gave a normal sugar tolerance on two occasions, three weeks apart and the tuberculin reaction was positive. He also had a psoas abscess.

CASE 50—Lieutenant Gibson, aged 33, white, had no previous attacks. Present attack began in the fall of 1918, involving the left knee and shoulder and later other joints. Tonsillectomy was performed November, 1918, and he had no foci on admission. This case ran a refractory course and gave a moderately elevated sugar tolerance curve which later fell to normal, following nonspecific protein injections. Improvement resulted as described under "Studies on the Blood Sugar" and "Clinical Considerations." The protein injections were accompanied by marked facial herpes.

CASE 51 (No 3797)—Lau, aged 27, white, had no previous attacks. Symptoms dated from gassing and high explosives Sept 30, 1918, and were never clearly rheumatic, although possibly truly so. One site of pain was above the costal borders posteriorly, this region was very tender to touch. This was noticed in other patients also. He had eczema of the hands and chronically diseased tonsils. Following an injury in mid-boyhood, one testicle was transplanted with apparently subsequent atrophy. This soldier showed loss of secondary sexual characteristics and grew much fatter in the hospital. He presented a very low sugar curve, that is, a high tolerance. There was probably a mild neurotic element. Tonsillectomy was not followed by noteworthy change.

CASE 52—Lieutenant Lynch, aged 33, white, had no previous attacks. Present attack began August, 1918, but he recovered. He again became acutely and more severely sick, Oct 30, 1918, with pains in the feet, knees, right hip, elbow and jaw. He ran a very refractory course and became crippled all over, including the spine and back region. He improved under dietetic measures, and tonsillectomy, as is fully described under "Dietary Considerations." The sugar curve, March 22, 1919, was lower than his clinical condition suggested a priori, but his tonsils proved negative for *Streptococcus hemolyticus*. Subsequent to this test and the tonsillectomy, he developed a severe iridocyclitis but eventually was well started toward recovery.

CASE 53—Mrs K, Red Cross worker, aged 47, for some years had various arthritic disability and deformity of all finger joints. She had tonsillar and dental foci March 22, 1919, and gave a high sugar curve. This case was carefully studied and presented several points of interest. Tonsillectomy was performed April 2. Five days later, after two days of sharp unintended low feeding, her hands showed marked improvement. On resuming her full diet the previous condition returned in all its severity. She then developed acute catarrhal jaundice, with extreme obstipation and fecal impaction. During ten days of extremely low diet, necessitated by nausea, her joint condition entirely cleared up again and remained so until she again was eating as before. Her phalangeal arthritis then returned. Dental treatment was postponed until further recovery of strength. She disappeared from observation on closure of the hospital. This case illustrates the definite improvement coincident with postoperative starvation as frequently emphasized by me previously and further exemplified by Case 52 (Lynch). It also illustrates the occurrence of this improvement in the presence of infection (dental foci and probably also infection associated with the catarrhal jaundice). Compare the

improvement of Oberg (Case 22) under low diet in the presence of tonsillar infection as described under "Dietary Considerations" It is particularly to be noted that the arthritis returned twice in her case after twice disappearing under low feeding (Compare similar return in Case 52, Lynch)

CASE 54—Miss A, aged about 59 years, studied by permission of the commanding officer and in conjunction with Lieutenant-Colonel Gittings, had an arthritis of some years standing, affecting her hands March 26, 1919, she gave a somewhat elevated sugar curve which returned very slowly to its original level She had been pronounced free from focal infection

CASE 55—Cotter, aged 33, white, had no previous attack Present attack began Nov 30, 1918, following a hike, with disability in the back, and the right hip, which became stiff and painful to motion and pressure His symptoms were subacute He had a tonsillar focus, gave a normal sugar tolerance April 2, 1919, and was apparently not greatly benefited by tonsillectomy or protein injections There was difficulty in relating his normal sugar curve to his subjective complaints There were no visible evidences of trouble, but this curve may have been an exception to the usual findings

CASE 56 (No 5165)—Kearly, aged 52, white, had no previous attacks The present attack began Nov 20, 1918, with pains in the left hip, knee and foot He walked with much difficulty, and his left big toe showed bony overgrowth objectively and roentgenographically On admission this patient thought he was improving, following a furlough home, where he received treatment by sweats He gave a practically normal sugar tolerance and refused tonsillectomy, which was indicated, but he did distinctly improve and finally walked quite freely up and down stairs When this improvement was fairly established, an abscessed tooth was extracted which may have been of further assistance to his recovery The normal tolerance of this patient may be another marked exception to the usual findings or referable to the distinct progress toward recovery

CASE 57—Longenberger, aged 21, white, had no previous attacks Present attack began Nov 27, 1918, in the left knee, following exposure The course of his disease was very refractory, and he gave a distinctly lowered sugar tolerance He apparently was free from any foci anywhere, his tonsils having been removed Feb 5, 1919 This was without any effect May 15 One injection of nonspecific protein had also failed to benefit him This is one of a number of cases in which reduced diet should have been instituted, but closure of the hospital prevented further treatment

CASE 58 (No 5233)—Bruno, aged 21, white, had no previous attacks Present attack began November, 1918, in the knees and ankles, following exposure He had positive tonsil and dental foci, but after being in bed one month he made a good recovery and was free from symptoms May 16, 1919, when he gave a moderately elevated sugar curve No foci had been removed and he had been well for one month

CASE 59 (No 5252)—Flanders, aged 27, white, had inflammatory rheumatism when 13 years of age, and very slight pains in January, 1918, but he was not confined to bed A bad tooth was extracted two years previously Present attack began Nov 15, 1918, with stiffness and pain in the legs, ankles, feet, left shoulder and hips, with swelling of the feet but no fever He was in bed one month and on admission had made a considerable recovery, but the heels under the Achilles tendons were very tender to pressure and motion He thought his condition was stationary for six weeks past He gave a sugar tolerance definitely but not markedly below normal, the curves showing a tendency to remain elevated

The roentgen-ray examination was positive, and he had foci in his teeth and tonsils Closure of the hospital prevented final data in this case, but he was evidently on the way to recovery There was no removal of foci

CASE 60 (No 4804) —Herron, sergeant, aged 24, white, no previous attacks Present illness began May, 1917, following appendiceal abscess with pain in the hips, fingers and knees Following a sharp exacerbation about May 15, 1919, accompanied by fever, as described under "Clinical Considerations," he gave a greatly lowered sugar tolerance, although at that time he was free from symptoms He had been treated by acetylsalicylic acid but had received none on the day of the test In the early course of the present illness he had been benefited by treatment at Hot Springs, Ark Repeated examinations made at U S Army General Hospital No 9 failed to reveal demonstrable foci Closure of the hospital prevented further observation

CASE 61 (No 5313) —Harry Miller, aged 22, white, had slight rheumatic pain in the left leg three years previously Present attack began April, 1919 with disability in the heels and in the right knee He was admitted from his command and while in the hospital he developed a sharp exacerbation with fever, pain and swelling He had foci in the tonsils, which were removed April 29 Eight days previously, during this exacerbation, he showed a very high sugar curve, which was still high three days later when his symptoms were relieved by acetylsalicylic acid Twelve days after the tonsillectomy he had another sharp exacerbation, with fluid in the right knee and pain in the neighboring muscles May 13 two weeks after the tonsillectomy, and when convalescing from the exacerbation just mentioned, he gave a much lower sugar curve, indicative of a marked return of the sugar tolerance toward normal although it was still slightly elevated, to 0.167 per cent Closure of the hospital prevented following this case further

CASE 62 —McKensie, aged 20 white, had rheumatic fever when 10 years old, another attack in 1918, and three other mild attacks thereafter, five attacks in all This case is described under "Observations on the Blood Sugar" as an instance of markedly lowered sugar tolerance during rheumatic fever He had a dental focus After recovery from the inflammatory attack, for which he was admitted, he again developed an attack with fever He refused dental treatment, but recovered symptomatically under medication and was discharged on the closure of the hospital He gave a double plus Wassermann reaction (army standard)

CASE 63 (No 4919) —Folden, aged 24, white, for ten years had been subject to arthritic pains in the right leg Present illness began gradually in June, 1918 in first the right leg and arm later involving the elbow and shoulder, following exposure This soldier had really never been well since his induction into the army, although he recovered sufficiently overseas to receive a gunshot wound going over the top He illustrates the type of person who should be rejected in the draft or preferably segregated for removal of disease producing factors He had tonsillar foci of infection which were removed April 24 as he was still invalided then May 12, eighteen days later he had a sharp exacerbation of his symptoms, with enlargement and tenderness of the leg simulating phlebitis This is described under "Clinical Considerations" Closure of the hospital prevented further observation

CASE 64 (No 3689) —Harry Fisher, aged 23, white, one month before entering the army had rheumatism in the elbow, shoulder, fingers and ankle Present attack began December, 1918, following exposure in the trenches and affected his feet and hands There were foci in the tonsils and positive roentgen-ray findings On admission he had made a limited improvement, but later he developed a severe rheumatic iridocyclitis because of which tonsillectomy was postponed Shortly thereafter he disappeared from observation on closure of the hospital

CASE 65 (No 5245) —Gale, aged 28, white, had no previous attacks Present attack began Sept 15, 1918 about coincidentally with an abscess of jaw following tooth trouble and affected his right leg, hip and knee, and later

his hands. He was much benefited by warm baths at Aix and made a considerable recovery in the presence of a tonsil focus. This was later removed with much further benefit.

CASE 66—Basits, aged 20, white, was taken sick overseas with trouble in his left ankle which later was incised. After improvement his left knee grew painful, it became very large and fluid accumulated in it. It was regarded as tuberculous but repeated guinea-pig injections overseas and in this country proved negative. Tuberculin injections caused a marked febrile rise and made him distinctly worse. Dental and tonsil foci were removed without obvious improvement. After applying a cast, the condition subsided somewhat. Closure of the hospital prevented further observation. This case illustrated that cases may strongly suggest tuberculous conditions without being so. Other instances of the kind indicated that tuberculous arthritis may not be as frequent as has been supposed.

CASE 67 (No 3550)—Burgess, corporal, aged 23, white, had no previous attacks. He had dysentery in August, 1918, lasting seven days. It never recurred. He spent one week in a convalescent camp and then suddenly developed rheumatism of the right wrist, left hip and both knees. He was in bed two and one-half months. This case illustrates the occasional late onset following infection described under "Clinical Considerations." Convalescence was slow but practically complete. The tonsils had been removed when he was 12 years of age. This case apparently ran its entire course in the absence of demonstrable surgical foci.

CASE 68—Lieutenant Turner, aged 31, white, had one previous attack in 1917. Present attack began gradually about Sept 1, 1918. About October 25 he reported sick, with involvement of his ankles, feet, elbows, shoulders and knees. Tonsillectomy was performed Feb 18, 1919, when he had recovered except for involvement of one knee. Only limited improvement followed, and protein injections were necessary two months later. These helped slightly. On discharge, his condition was only intermittently active.

CASE 69 (No 4481)—McIntyre, sergeant, aged 21, white, had no previous attacks. While in a German prison camp he developed "meningitis," Oct 1, 1918. Following recovery he had stiffness and tenderness in the back, with some symptoms in the left wrist. He had foci in his teeth and tonsils and tonsillectomy was performed April 9, 1919. One tooth was extracted. Diminished tenderness was noted five weeks later, he also had marked flatfoot from invalidism. The back was flattened over the lower half, and this case constituted one of the dorsal type difficult of diagnosis. The tonsils were negative for *Streptococcus hemolyticus*.

CASE 70 (No 3809)—Fontanella, aged 20, white, had no previous attacks. Present attack began gradually in October, 1917, following exposure. He remained on full duty until March when he was put on light duty. May 24 he was sent to the hospital. This man presented a wide female type of pelvis. He was taken sick in the presence of tonsillar and dental foci. One tooth was extracted about April 1. Two tuberculin tests were negative. His chief complaint was dull pains in the left leg and later in the back. A mass was palpable to the left of the vertebral column posteriorly, diagnosis apparently was Pott's disease. His function improved much after application of a brace. This case illustrates the difficulties of diagnosis, unless qualified orthopedic help is available.

CASE 71 (No 4567)—Crawford, corporal, aged 30, white, had one attack in 1913 in his hip. Present attack began in September, 1917, following exposure. Tonsillectomy was performed the same month without benefit so far as the mild symptoms were concerned. The distribution was left hip, right ankle, back and occasionally other joints. The arthritis grew worse in October. In January, 1919, he had a tooth extracted also without benefit. This case was

very severe. The man became bed-ridden and developed edema of the ankle. He was too sick for radical treatment and on closure of the hospital he was transferred to Hot Springs, Ark.

CASE 72—Barkely, aged 27, white, had no previous attacks. He had tonsillitis in November, 1917, erysipelas in January, 1918, pleurisy in March, 1918, pericarditis in April, 1918, mild ear trouble in August, 1918, at which time the wrist became involved. The wrist grew worse in December, 1918, with swelling and some tenderness and a heel ulcer developed in January, 1918. The fluid contents were sterile. The ulcer refused to heal and the wrist made little or no progress. Tuberculosis was a strong possibility, but was not proved. This case had tonsillar and dental foci which were removed. The Wassermann test and roentgen-ray examination were negative. On the orthopedic service.

CASE 73—Lieut. Jordan, aged 23, white, had no previous attacks, but had frequent attacks of tonsillitis during last two years. Present attack began in the right hip, right sacroiliac joint and lower lumbar vertebrae about Sept. 1, 1918. Tonsillectomy was performed April 2, 1919. He improved but was still greatly disabled. Further observation was prevented by closure of the hospital. This case illustrates the repeated delay observed in instituting the proper therapy.

CASE 74 (No. 5351)—Curley, aged 32, white, had no previous attacks. The present attack began about Feb. 1, 1918, involving the legs, back, hips, knees, ankles, right shoulder and neck following exposure. Tonsillar and genito-urinary foci were present. He was apparently improved by prostatic massage. Tonsillectomy was performed April 12, 1919.

CASE 75 (No. 4828)—Dion, sergeant-major, aged 30, white, had no previous attacks, but he had a sore throat nearly every year. Present attack began in January, 1918, with pains in the knees and feet, following exposure. His tonsils were removed March 24, 1919, and he also had a dental abscess. This case resembled Case 10 (Masood), Case 14 (Lowe), and Case 15 (Studebaker) in the exquisite tenderness on light touch over the legs and feet, and absence of objective evidences. Closure of the hospital prevented final observation.

CASE 76—Miss H., aged 45, army nurse corps, had no previous attacks. She was taken sick suddenly Jan. 1, 1919, with rheumatism of the left shoulder and right hand. On admission her chief trouble was in the right sciatic region and in the left shoulder. She was reported definitely to have no foci of infection and after remaining stationary for some months she showed marked and gratifying improvement under restricted diet as detailed under "Dietary Considerations." A genito-urinary examination was not made.

CASE 77 (No. 5443)—Lieutenant Morris, aged 24, white, had no previous attacks. He was taken sick in August, 1918, with involvement of his left hip and later the left foot, both knees, hips and shoulders and one finger. He had dental, tonsil and genito-urinary foci. An abscessed tooth was drained without benefit in September, 1918. March 27, his tonsils were removed with good results and he received treatment for prostatitis. Six weeks later he was better but he was not well on closure of the hospital.

CASE 78 (No. 4997)—Kirkwood, aged 23, colored, had no previous attacks. December, 1918, he developed rheumatism of the ankles, knees, right hip, right wrist and back. He was in bed three weeks with fever, much swelling and pain. He had a gonococcal infection in August, 1918. The only infection was located in the genito-urinary tract and this case may have been of gonococcus origin, although this is uncertain. He had made considerable improvement along expectant lines and was further benefited by genito-urinary treatment but was not well on the closure of the hospital.

CASE 79—Cox, aged 36, white, had no previous attacks. He had rheumatism of several joints following exposure in the trenches, and was struck on the wrist with a musket Feb. 21, 1918. He then became stiff in every joint within a few days. All symptoms subsided, except in the wrist. On

admission he was found to have a fracture of one carpal bone. Removal of fragments and immobilization was followed by improvement and eventual subsidence, leaving a small range of motion. The reaction in the wrist following operation, however, was atypical and was regarded by Major Cleary of the orthopedic service as due to a rheumatic condition. There was undoubtedly some slight rheumatism elsewhere. He had foci in the tonsils.

CASE 80 (No 4479)—Spatarro, aged 32, white. No previous attacks. Present attack began in August, 1918, with pains in the left wrist which became swollen. He went to the hospital in November and remained there. The roentgen ray showed one carpal bone to be markedly rarefied. There were no foci anywhere. The case was thought to be tuberculous but a negative tuberculin reaction was obtained. This seems to be an atypical example of true arthritis. A cast was advised when the hospital closed and he was transferred elsewhere.

CASE 81 (No 3312)—Schoonover, aged 24, white, had no previous attacks. He did full duty in the infantry until he was gassed in August and sent to the hospital. He had been exposed to cold and wet before then, and had stiff joints as a result. In October, however, he was for the first time seriously afflicted with rheumatism which came on while in the hospital, first involving the right hip and right knee, then both shoulders. He was in bed October and November, then improved, but the right knee remained in statu quo with some symptoms at other points occasionally. He had a tonsillar focus which was removed although no marked influence could be seen on the arthritis in two and one-half months.

CASE 82—Lieutenant Keys, aged 33, white, had rheumatism in 1914 and 1916. Present attack came on Jan 2, 1919, involving the right shoulder, back, knees and other joints. He had foci in the genito-urinary tract and tonsils. When considerable improvement had occurred, tonsillectomy was performed. He continued to improve further and also received treatment for the genito-urinary condition. The tonsils were negative for *Streptococcus hemolyticus*. This case was regarded by Capt George Smith, chief of the genito-urinary department, as one of the few cases apparently due to genito-urinary infection. His further improvement seemed to relate somewhat to treatment of this.

CASE 83—Mrs G, aged 50, white, was studied by permission of the commanding officer. She had suffered for some years with a progressive arthritis of her hands, knees, shoulders and feet. She had her tonsils and all other foci removed two years before without any real benefit.

CASE 84 (No 1275)—DeKim, sergeant, aged 42, white, had no previous attacks. Present attack began gradually in January, 1918, involving the left shoulder, hip, knee, ankle and spine, following exposure. The knuckles of the hand were enlarged and headache was a persistent symptom. Received frequent protein injections without benefit.

CASE 85—Leeman, aged 18, white, had no previous attacks. Present attack began in October, 1917, involving the feet, following exposure. Several teeth were extracted in France. Had foci in his tonsils which were removed and found diseased. This man had great tenderness in the metatarsophalangeal joints of the feet, and had not been able to walk for a year. By the date of tonsillectomy he had greatly improved but this operation benefited him further. The loss of time in this case and the propriety of tonsillectomy a year sooner are to be noted.

CASE 86—Zuch, aged 28, white, had no previous attacks. Present attack began in April, 1918, with pain and redness of the hip, knee and shoulders, following exposure and injury to the left hip. His case ran a chronic course. He recovered except for the left hip and knee. A small fracture in the head of left femur was found. The roentgen ray gave definite evidence of arthritis elsewhere. No foci were detected although the tonsils were submerged and may have constituted foci.

CASE 87—Sharpe, aged 47, white, had previous trouble in his back. Present attack began in March, 1918, involving sacroiliac region, following exposure to damp. He had abscessed teeth and was discharged with mild disability shortly after the inauguration of the arthritic service. He was instructed to have the offending teeth removed.

CASE 88—Bartkiavicus, aged 26, white, had one attack in 1914. Present attack began in July, 1918, involving the right shoulder, left ankle and hips, following gas poisoning. He had tonsillar foci which were removed Dec 13, 1918, after he had made a full recovery.

CASE 89—Cichon, aged 22, white, had had slight recurrent attacks. Present attack began July 29, 1918, in the wrists and hands, following exposure. He had foci in his teeth but made an essential recovery before their removal.

CASE 90—Mulledy, aged 21, white, had rheumatism for three years at intervals. Present attack began in September, 1918, in the left ankle, knee, hip, shoulder and elbow. Most of these joints were red and swollen. A tonsillectomy was done Nov 1, 1918, and was followed by slow improvement. On discharge, January 2, his symptoms were trifling and intermittent.

CASE 91—Saxton, aged 24, colored, had had no previous attacks. The present attack involved the knees and ankles. There was apparently no focus and he was treated with repeated vaccine injections with alleged good results.

CASE 92—Kolden, aged 26, white, had an attack in 1910 lasting eight months. Present attack began acutely Nov 21, 1917, in the knees, ankles, back and right hand. Tonsils and a root abscess were removed without marked benefit. History incomplete.

CASE 93—Hamburger, aged 23, white, had no previous attacks. Present attack began January, 1918, following exposure. He improved and then relapsed in May, 1918, many joints and his back being affected. He had foci in tonsils and teeth and had convalesced considerably when admitted except for slight tenderness in the left hip and knee. Removal of foci was followed by disappearance of residual symptoms and this soldier was still well in June, 1919.

CASE 94—Meadors, aged 23, white, had no previous attacks. Present attack began Jan 14, 1918, in the wrists, elbows, hips and shoulders. He had foci in his tonsils which were removed Sept 28, 1918. In February he had made slight progress, but had many painful joints in his hands. He was further improved by nonspecific protein injections and was discharged about well.

CASE 95 (No 4901)—Tingue, aged 27, white, had a previous attack when 14 years of age. Present attack began in August, 1918, overseas during an attack of dysentery. The knees and later the hips and left shoulder became involved, and he made a slow and limited improvement. He had foci in his tonsils which were removed May 7, 1919. At closure of the hospital, June 1, the elapsed time did not permit of reliable data as to his progress. See "Clinical Considerations," Part V.

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# A RESEARCH ON BLOOD SUGAR IN DEPANCREATIZED DOGS \*

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Recent experiments on the intravenous injection of epinephrin in normal dogs give rise to a question of considerable interest. If the injection of epinephrin causes a temporary hyperglycemia in normal animals, the blood sugar increasing shortly after injection, what would be the result in animals from which the pancreas has been removed? On this idea of investigation, these series of experiments were commenced. The intravenous injection of epinephrin in man has shown, in addition to a temporary hyperglycemia, in some cases a decrease in the output of carbon dioxide from the lungs, which supports the theory that epinephrin inhibits the combustion of sugar in the body, in opposition to the school that believes epinephrin increases the blood sugar by increasing the output of glycogen from the liver. At least, it seemed probable in undertaking this work that a relationship or antagonism might be determined between the pancreas and epinephrin toward the metabolism of the sugar in the body.

My procedure in carrying out a number of experiments to this end was to depancreatize completely a dog and inject a given amount of epinephrin several days after operation, after injection withdrawing the blood at regular intervals, from four minutes to one hour, for the purpose of the blood sugar determination.

The method of removing the pancreas was one of dissecting it away from the mesentery in which it is enveloped. It is not difficult to ligate the minute vessels leading to the gland from the duodenal artery and vein, which can be dissected out carefully without destroying the circulation to the duodenum, and at the same time all the surrounding pancreatic tissue separated from them intact with the pancreas. At least one layer of mesentery can be preserved, except a small area about 3 cm in diameter, where the pancreatic duct enters the duodenum. However, the preservation of a large portion of the duodenal mesentery seems to be of little importance, as adhesions will form about the duodenum. In a satisfactory number of dogs, the adhesions did not interfere with the function of the intestine, or cause obstruction, waiting a sufficiently long time after operating before following out the experiments.

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\* This work was done in the laboratory of Prof C Achard with Mm A Ribot and Leon Binet, whom I thank for their council in the work.



The greatest difficulty encountered in removing the pancreas was in the region of the splenic artery and vein, where, in order to avoid hemorrhage, there is danger of leaving a small portion of the gland

Six dogs were operated on for removal of the pancreas by the method described above. Two died from postoperative hemorrhage, one twenty-four hours, the other forty-eight hours after operation. One animal died three days after operation, owing to obstruction from adhesions formed about the duodenum.

If any pancreatic tissue is left behind, the blood sugar is certain to give indication of the error. One dog (B) forty-eight hours after operation showed a blood sugar of 2 gm per thousand cc, and two days later when the blood was withdrawn for examination it showed approximately a normal sugar content (1 gm per thousand cc). This animal was killed twenty-one days after operation. Dense adhesions were found in the region of the pylorus and duodenum. In spite of the adhesions, the duodenum had functioned well. For fifteen days the dog had been eating the usual diet of meat, stew and rice. At necropsy a search was made for pancreatic tissue, and after a prolonged examination a small piece of tissue, not exceeding in size half that of a hazel nut, was found in the region of the postmesenteric glands. Two other dogs that were operated on continued to show a hyperglycemia. One of these animals (Dog A) died the tenth day after operation, and the other (Dog C) was killed twenty-four days after pancreatectomy. No pancreatic tissue could be found in either of these animals at autopsy.

Those animals from which nearly all of the pancreas is removed, usually showed a hyperglycemia the first two or three days after operation. They may be useful in that time to observe the effect of intravenous injection of adrenalin upon the blood, but not after the blood sugar has returned to normal, as we then have quite the same condition as in normal dogs. In Dog B (Table 1) we have an example of this, as four days after operation the blood sugar was normal, and incomplete removal of the pancreas was found at necropsy. Two days after operation the blood sugar was double the normal amount. It does not concern this particular work whether the small amount of pancreas left in the body was insufficient, together with the shock of the operation, for the first couple of days, to take over the glycogenetic function of the pancreatic tissue removed, or whether in a few days the remaining pancreatic tissue hypertrophied sufficiently to take up the glycogenetic function of the pancreas. But it is quite certain that the hyperglycemia existing in dogs up to the time of their death, from ten to twenty-four days after operation, was not due to the operation.

per se, but to an absolute removal of the pancreas, as sufficient time had elapsed for any remaining tissue of the gland to reestablish its function

As will be seen in Table 1, in the normal dog (Dog A) there was a marked rise of sugar in the blood, after the intravenous injection of epinephrin. Whether epinephrin inhibits the metabolism of sugar in the body or tissues, or whether it augments the output of glycogen from some organ is of great interest, but difficult to determine absolutely. The decrease in the output of carbon dioxide after the administration of epinephrin is injected in man speaks strongly for the increase in blood sugar being due to an inhibition on the part of epinephrin to the burning of the sugars in the tissues.

TABLE 1—RESULT OF INJECTION OF EPINEPHRIN IN NORMAL AND DEPANCREATIZED DOGS

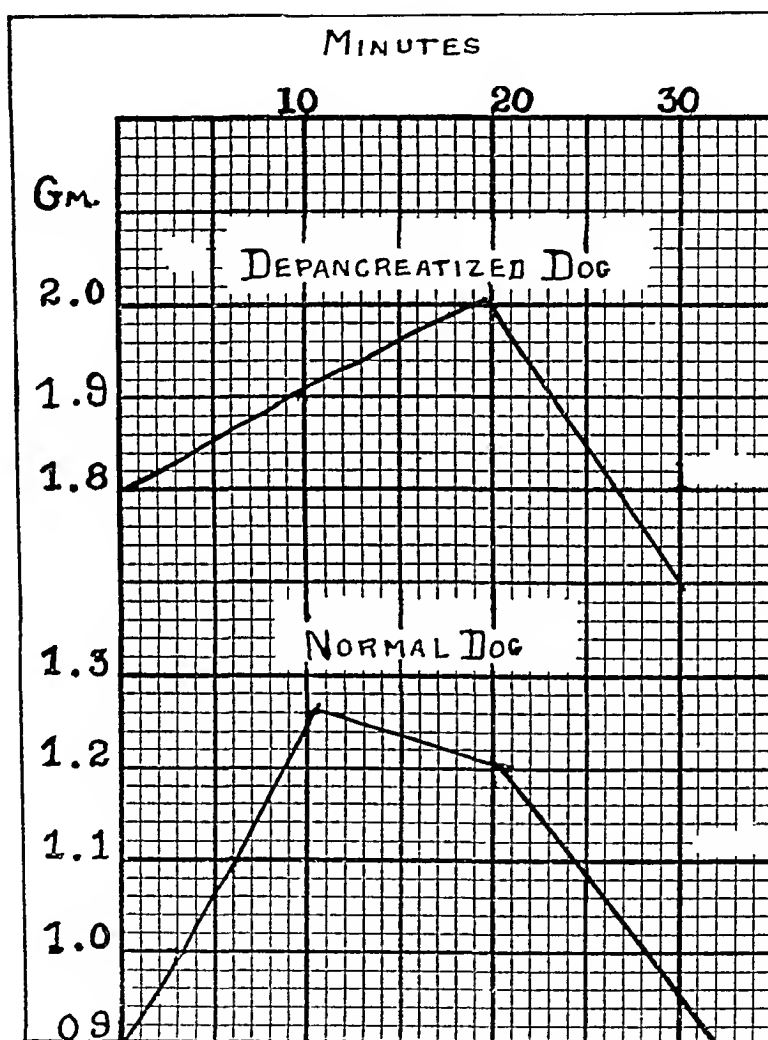
Dog		Amount of Epinephrin Injected	Blood Sugar, Gm per 1,000 C c				
			Before Injection of Epinephrin	Minutes After Injection of Epinephrin			
				10	20	30	40
A	Before depancreatization	1 mg	0.95	1.25	1.20	0.95	
A	After depancreatization	1 mg 1 day after operation	1.80	1.90	2.00	1.65	1.55
B	After depancreatization	2 mg 4 days after operation	1.00	1.30	1.50		
C	After depancreatization	2 mg 11 days after operation	3.00	3.00	3.00	3.10	

In Dog A the rise of blood sugar after epinephrin injection proportionately was not as great after depancreatization as before, and the fall to the previous sugar level was more abrupt than in normal dogs. This can plainly be seen by a comparison of the two curves. We also see the rise in blood sugar of the dog when depancreatized was much slower after injection than in a normal dog.

In Dog B, where a very small portion of the pancreas had been left in the animal, the rise in blood sugar after injection was quite similar to that of a normal dog.

In Dog C the injection of epinephrin after operation had practically no effect on the blood sugar. There was not any rise in the blood sugar observed in this depancreatized dog, as in the normal animal. One would suppose that if epinephrin inhibits the metabolism of sugar in the tissues in normal dogs it would do likewise in depancreatized dogs, and thus produce a higher blood sugar, by allowing sugar to pass into the circulation unburned. But in depancreatized dogs there

is a constant hyperglycemia, showing by our experiments very little or no rise by the injection of epinephrin. By removal of the pancreas, it seems quite possible that something has been removed favorable to the combustion of sugar in the body, and in depancreatized dogs the blood sugar is increased permanently in the way that it is increased temporarily after injection of epinephrin in normal dogs. The sugar



Blood sugar in grams per thousand cubic centimeters after injection of 1 mg of epinephrin

is passing into the circulation unburnt, as the influence favorable to the combustion of the sugar has been removed. If in depancreatized dogs, sugar passes into the circulation and is not broken down by the tissues, then epinephrin by injection can have no further action in inhibiting the metabolism of the sugars and be capable of producing much of a rise in blood sugar. It would seem that the pancreas has

exactly the opposite effect of epinephrin on the metabolism of the sugars in the tissues, the pancreas augmenting, the epinephrin inhibiting<sup>1</sup>

Dogs injected with sugar intravenously show some difference before and after depancreatization in the rapidity of reducing additional sugar added to the blood

TABLE 2—FIVE GM OF GLUCOSE IN SOLUTION INJECTED INTRAVENOUSLY

	Blood Sugar, Gm per 1,000 C c					
	Before Injection	Minutes After Injection				
		10	20	30	40	50
Normal dog	1 15	1 35	1 15	1 15	1 15	
Depancreatized dog 48 hours after operation	2 00	3 00	2 6	2 7	2 45	2 35

In each case, that of the normal and depancreatized dog, the tables show the result in blood sugar expressed in gm per thousand c c after equal amounts of glucose have been injected. The dog without pancreas had a slower fall in blood sugar than the normal animal. In other words, the normal dog showed a greater ability to handle the added amount of sugar than the dog without the pancreas. If the pancreas did not play a part in the metabolism of sugar in the body we would expect the blood sugars after the injection of glucose to fall to their former respective levels with about the same rapidity. If the glycogenetic function of the pancreas was merely to control the output of glycogen from the liver, the removal of the pancreas ought not to interfere with the handling of an added amount of sugar to the blood. But Table 2 shows that the fall in blood sugar to the level before injection is not as rapid as in the depancreatized dog.

#### SUMMARY

1 Complete removal of the pancreas produced a permanent hyperglycemia, and any part of the pancreas left in the animal after operation later manifested itself by a fall in blood sugar.

2 Epinephrin by intravenous injection in normal dogs increased the blood sugar. With the pancreas removed, epinephrin produced

<sup>1</sup> It may be possible in life that the pancreas acts as a check on the output of epinephrin from the suprarenal glands, and that with the pancreas removed there is an excessive production of suprarenal secretion put out into the circulation, thus inhibiting the metabolism of the sugars and allowing them to pass unburnt into the circulation. Examination of the suprarenals of one person dying with diabetes and two depancreatized dogs showed a very low epinephrin content by the Folin colorimetric method for quantitative examination of epinephrin. *J Exper Med* 19 536, 1914

very little, if any, change in the blood sugar Under this condition, as a possible explanation, sugar is passing freely into the circulation unburnt, and therefore the epinephrin can have very little further effect in increasing the blood sugar by inhibiting sugar metabolism

3 It is reasonable to believe that the pancreas produces some substance which favors the metabolism of the sugars in the tissues, as sugar injected intravenously is not handled as readily in the depancreatized animal as in the normal dog

# THE PROGNOSTIC VALUE OF CHOLESTERINEMIA IN CHRONIC NEPHRITIS

## FINAL REPORT

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MILWAUKEE

In a preliminary report on this subject,<sup>1</sup> I presented a number of cases to show that a hypercholesterinemia is usually to be found in cases of chronic nephritis which are progressing favorably, and that a normal or subnormal figure for the serum cholesterol, in cases of chronic nephritis, is of distinct prognostic importance and value. The measure of cholesterinemia in the cases enumerated in my early paper accurately foretold the prognosis in individual cases.

The study of the chemistry of the blood has made giant strides during the past few years, and we are now enabled to measure accurately, especially the nonnitrogenous constituents of the blood — total nonprotein nitrogen, urea nitrogen, creatinin, uric acid and sugar. There seems to be little disagreement as to the best quantitative methods to employ, and the clinician has a right to accept the quantitative determination without a doubt.

Much work along this line has been done, but notably in nephritis and diabetes mellitus, conditions in which the carbon dioxide combining power of the blood is of exceedingly great value from a prognostic standpoint.

While there is no doubt that the study of the prognosis in chronic nephritis must, of necessity, be associated closely with those chemical metabolic products which the kidneys normally excrete, and which, in the event of functional decompensation, are excreted with increasing difficulty, resulting in a corresponding increase of these same substances in the circulating blood, there is evidence to show that the uremic death of nephritics is due to a severe acidosis. The marked fall in the carbon dioxide combining power of the blood in uremia is a striking proof of this, and it has been my belief for many years that the lipid substances of the blood are intimately associated in the chemistry of acidosis.

With the advent of so-called "blood chemistry," investigators actually plunged into the study of chronic nephritis with exceedingly valuable results. I have always insisted, however, that the study of cholesterinemia in chronic nephritis was equally as important, if not more

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1 New York State M. J. 15 300 (Aug.) 1915

so, in an endeavor to prognosticate in any given case. The work begun in 1914 was, therefore, continued. It is my purpose to show how intimately associated are the study of the cholesterinemia and the study of the nonnitrogenous products of the blood in chronic nephritis, and at the same time, to add further weight in substantiation of my preliminary report on the subject.

Reference to the preliminary report will show that the measure of cholesterinemia in the individual cases presented foretold the prognosis very accurately in each case. It is to be remembered that the cholesterinemia must be interpreted properly in each case, and allowances must be made for any coincident clinical conditions that experience has taught us tend to increase or decrease the amount of cholesterol in the blood. The early report showed that a hypercholesterinemia is present in all cases of chronic nephritis, and that the measure of cholesterinemia decreases as the uremic state is approached. All cases of uremia, and all cases terminating fatally in coma, showed a most decided hypocholesterinemia.

Since the introduction of blood chemistry, the functional ability of the kidneys has been studied in terms of the retention in the blood of the total nonprotein nitrogen, urea, creatinin and uric acid, and the carbon dioxide combining power of the blood serum. Our studies have shown that evidence of increasing retention in the blood of the products just enumerated is of prognostic importance, and rather accurately foretells an impending uremic state.

The blood figures generally recognized as being the normal for the blood constituents enumerated, are as follows:

Total nonprotein nitrogen, from	25	to	35	mg	per hundred	cc
Cholesterol, from	150	to	180	gm	per thousand	cc
Urea nitrogen, from	12	to	18	mg	per hundred	cc
Uric acid, from	08	to	25	mg	per hundred	cc
Creatinin, from	08	to	2	mg	per hundred	cc
Sugar as glucose, from	008	to	015	per	cent	

Any increase in the figures mentioned is to be regarded as evidence of retention of these products, but in speaking of cholesterol, it is probably not correct to speak of it as being retained, for, in the normal individual it is not a product of excretion. When figures as high as 80 mg of nonprotein nitrogen per hundred cc of blood are obtained, a very definite evidence of retention of these waste nitrogenous products is indicated. When figures as low as 1 gm of cholesterol per thousand of blood are obtained, they are distinctly below normal, especially in a condition where a decided increase is to be expected. It is just this normal, or subnormal figure for the cholesterol in chronic nephritis, which is of such interest and importance.

## REPORT OF CASES

The following cases will show the prognostic import that can be attached to the measure of cholesterinemia in chronic nephritis

CASE 1—Male, aged 66, no jaundice, no fever, moderate arteriosclerosis, blood pressure, 220, Wassermann reaction, negative, urine contained albumin, hyaline and granular casts. The general condition of the patient was not very good at the time the blood was examined. Examination of the blood showed urea nitrogen, 55 mg, uric acid, 27 mg, creatinin, 1 mg, and sugar 0.132 per cent, while the cholesterol was 2.05 mg.

Under the clinical circumstances one would expect a much higher cholesterol figure. The absence of a decided hypercholesterinemia in this case should make me suspect a moderate degree of retention, and the figures for the nonnitrogenous products indicate that retention.

In presenting these cases, only relevant clinical states, as they influence cholesterinemia, are recorded. These clinical states are the following: (1) Fever reduces cholesterinemia, (2) jaundice increases cholesterinemia, (3) arteriosclerosis (active) increases cholesterinemia.

CASE 2—Female, aged 60, temperature, 100.8 F, no jaundice, slight arteriosclerosis, urine contained albumin, hyaline and granular casts, no edema, eye grounds negative, Wassermann negative. At the time the blood was examined, there were no symptoms suggesting an impending uremic state, but the cholesterinemia amounted to only 1.73 mg, a hypocholesterinemia under the circumstances. On the following day, a sudden delirium set in, the patient gradually went into coma and died two days later.

In this case, while there are no additional blood figures, I am reasonably sure that examination would have shown evidence of a decided retention of waste nitrogenous products.

CASE 3—Female, aged 59, was admitted to the hospital with a diagnosis of carcinoma of the stomach, although repeated roentgen-ray examinations failed to substantiate that diagnosis. The temperature was 98 F, the Wassermann reaction was negative, hemoglobin, 52 per cent, red blood corpuscles, 2,420,000, leukocytes, 9,200, polymorphonuclears, 66 per cent, no jaundice, urine showed evidences of nephritis.

Our attention was drawn to her when she began to vomit and became drowsy, although previous to this, the patient manifested no signs of an impending uremia. The blood figures were as follows: Cholesterol, 1.65 mg, nonprotein nitrogen, 1.25 mg, urea nitrogen, 100 mg, uric acid, 5.5 mg, creatinin, 13.4 mg, sugar, 0.129 per cent, carbon dioxide, 10 volumes per hundred c.c.

These figures certainly suggest a threatened uremia. The stupor continued, coma supervened and the patient died at the end of two days.

CASE 4—Male, aged 50, admitted to the hospital with a diagnosis of chronic nephritis, no jaundice, temperature, 99 F, Wassermann negative, blood pressure, 180, moderate arteriosclerosis, urine contained albumin and hyaline and granular casts, no edema, general condition good. The following figures were obtained: Phenolphthalein elimination 79 per cent, urea nitrogen, 17.5 mg, uric acid, 1.4 mg, creatinin, 1.5 mg, blood sugar, 0.09 per cent, and cholesterol 2.34 mg.



Having done well, the patient was discharged, but returned to the hospital a year later. On his second admission, he was restless, noisy, not mentally clear, had a motor aphasia, was drowsy and sleepy, but showed no convulsions. His blood pressure was 170/110, no jaundice, no fever, urine contained albumin and hyaline and granular casts.

We were here dealing with an undoubted case of threatened uremia, and the blood figures obtained verified the condition. They were nonprotein nitrogen, 110, urea nitrogen, 58, creatinin, 35, uric acid, 5 mg and sugar, 0.136 per cent, with a carbon dioxid combining power of 42 volumes per hundred c.c. The cholesterinemia amounted to 1.43 mg, a decidedly low figure, under the circumstances.

Two weeks later the general condition of this patient was somewhat improved, but at the end of another week, the general condition again became worse and the following blood figures were obtained: nonprotein nitrogen, 41 mg, urea nitrogen, 16 mg, uric acid, 1 mg, creatinin, 11 mg, sugar, 0.146 per cent, carbon dioxid, 48.5 volumes per hundred c.c. These are practically normal figures, but the cholesterinemia continued low, 2.02 mg. Subsequent work was not done in this case, but the patient, after some ups and downs eventually died in uremic coma.

**CASE 5**—Female, aged 61, was admitted to the hospital with a mild chronic nephritis and arteriosclerosis, no jaundice, no fever, blood pressure, 210, Wassermann, negative, urine, very faint trace of albumin and no casts. Eyegrounds showed neurochorioretinitis. A facial palsy, with a pure motor aphasia, justified the diagnosis of hemorrhage from the middle meningeal or middle cerebral artery.

The blood figures in this case were as follows: Urea nitrogen, 16 mg, uric acid, 27 mg, creatinin, 15 mg; sugar, 0.106 per cent, and cholesterol, 2.93 mg. These figures certainly do not suggest a severe chronic nephritis. Four days later, a sudden coma developed and the patient died. Death was most likely due to cerebral hemorrhage.

**CASE 6**—Male, aged 52, a case of chronic nephritis with undoubted uremic state, for when the blood was first examined the patient was in coma. Quantitative estimations of the nonprotein nitrogenous constituents of the blood at that time gave the following: Urea nitrogen, 35 mg, creatinin, 13 mg, sugar, 0.112 per cent, and carbon dioxid combining power, 31 volumes per hundred c.c., figures that surely do not indicate a very severe retention. There was no jaundice, blood pressure was 150, no edema and the urine showed albumin and hyaline and granular casts. The cholesterinemia amounted to 1.77 mg, a decidedly low figure under the circumstances. With sodium bicarbonate infusions the patient held his own for a few days, but a second examination of the blood failed to show the apparent gravity of the condition. The figures obtained were as follows: Urea nitrogen, 31, uric acid, 23, creatinin, 25, sugar, 0.12 per cent, carbon dioxid combining power, 48 volumes. Ten days later the patient died in coma. In this case, the relative hypocholesterinemia was of correct prognostic importance, while the measures of the nonnitrogenous constituents were not.

**CASE 7**—Male, aged 55, no jaundice, no fever, blood pressure, 170, moderate arteriosclerosis, Wassermann, negative, urine contained heavy trace of albumin, with hyaline and granular casts, general anasarca. Patient was restless, noisy and drowsy and a uremic state was certainly impending. Blood examination showed nonprotein nitrogen, 144, urea nitrogen, 85, creatinin, 6, uric acid, 10, sugar, 0.152 per cent and cholesterol, 1.85 mg. These figures bear out the severity of the condition. This patient grew steadily worse, delirium set in, and in two days he died in coma.

**CASE 8**—Male, aged 67. This patient was uremic and in very poor condition. The urine contained albumin, but no casts, and no acetone bodies. The blood pressure was 185. A pulmonary congestion was responsible for a fever.

of 101.5 F and a leukocyte count of 16,500. The figures for the blood were as follows: nonprotein nitrogen, 250; urea nitrogen, 150; uric acid, 10; creatinin, 187; sugar, 0.2 per cent and carbon dioxid combining power 15; cholesterol, 0.65 mg. At the end of twenty-four hours, muscular twitchings developed, the patient became stuporous, went into coma, and died. Figures before death (and without fever) were as follows: nonprotein nitrogen, 250; urea nitrogen, 166; uric acid, 10; creatinin, 18; sugar, 0.24 per cent; carbon dioxid combining power 44; and cholesterol 0.97 mg. These figures are typical of a uremic coma. At no time did this patient eliminate any phenolsulphonephthalein.

CASE 9—Male, aged 50, no fever, no jaundice, no arteriosclerosis, blood pressure, 200, Wassermann, negative, urine showed a large amount of albumin and hyaline and granular casts, dyspnea and general evidences of impending uremia, although the general condition of the patient was fairly good. Reasonably high figures for the waste products were found in examining the blood: nonprotein nitrogen, 55; urea nitrogen, 25; creatinin, 35; uric acid, 5; sugar, 0.2 per cent; phenolsulphonephthalein elimination 38 per cent. The high figure for the uric acid is certainly suspicious. A decided relative hypocholesterinemia, 1.45 mg was found. Ten days later, the patient became drowsy and stuporous and irrational and had to be tied in bed. Blood figures at this time, except for the cholesterol, again failed to show the gravity of the situation: urea nitrogen, 19; uric acid, 3.6; creatinin, 1.9; sugar, 0.10 per cent, while the cholesterol amounted to 1 mg, a very low figure under the circumstances. Two days later the patient went into coma and died.

CASE 10—Male, aged 27. This was a case of nephritis, based on syphilis, and despite the condition of the kidneys, was given vigorous antisyphilitic treatment. This patient did very well while under observation, and at no time showed any uremic tendencies. This case is reported to show the blood figures that are to be expected. There was no jaundice, no fever, slight general edema, the urine contained albumin and hyaline and granular casts, no headache, no vomiting, eyegrounds normal. Chemical examinations resulted as follows: Phenolsulphonephthalein elimination, 55; urea nitrogen, 15; creatinin, 1.5; sugar, 0.062 per cent, and cholesterol, 4.17 mg. Several months later the patient was under treatment in the dispensary, and was doing well. The cholesterinemia amounted to 3.49 mg at that time. This patient was eventually lost sight of, however, continued observation should include a periodic examination of the blood cholesterol, and if it should be found to be steadily decreasing, the prognosis would be correspondingly worse. This fact is demonstrated by the following cases.

CASE 11—Male, aged 35, no fever, no jaundice, no arteriosclerosis, blood pressure, 240, urine contained albumin and hyaline and granular casts, intense headache, suggesting brain tumor, nausea, vomiting and diminished vision (fundus showed albuminuric retinitis), no edema, no rigidity of the neck, phenolsulphonephthalein elimination, 40; urea nitrogen, 19; uric acid, 2.6; creatinin, 1.5; carbon dioxid combining power, 55; cholesterol, 3 mg.

Two weeks later, with little change in his general condition (with roentgen-ray examinations of skull and spinal puncture negative) and the blood picture remaining the same, the cholesterinemia was found to have fallen to 2.42 mg. At the end of another two weeks, the cholesterinemia had dropped to 1.80 mg. The general condition of the patient became steadily worse, another two weeks found him stuporous and drowsy and passing only from 300 to 500 cc of urine a day. At this time, with the temperature subnormal (95 F) and the picture of the urine unchanged, the cholesterinemia was found to be 1.10 mg. The following day, muscular twitchings set in, coma supervened and the patient died.

Necropsy revealed kidneys of a typical chronic interstitial nephritis. This case shows very well that it is the fall in the cholesterinemia that is of such prognostic importance.

The final case to be presented is one of exceedingly great interest. It is a case in which repeated examinations of the blood had been made, a case that had been carefully studied. The blood figures show well how the measure of cholesterinemia can be used in determining accurately the prognosis.

CASE 12—Male, aged 23, no fever, no jaundice, considerable edema, blood pressure, 194, eyegrounds, normal, urine shows many hyaline and granular casts, and a heavy trace of albumin, Wassermann, negative, no evidence of impending uremia. The blood, which was turbid and chylous, showed 797 mg of cholesterol, the highest figure I have ever obtained in a case of nephritis. At the same time, the blood showed nonprotein nitrogen, 770 mg, urea nitrogen, 24, uric acid, 23, creatinin, 53, sugar, 0.124 per cent. Two weeks later, with conditions practically the same, except for some languor, the following figures were found: Cholesterol, 502 mg, nonprotein nitrogen, 106, urea nitrogen, 55, uric acid, 7, creatinin, 13.6, sugar, 0.172 per cent, carbon dioxide combining power, 18 volumes per hundred c.c., blood indican, ++, and only a trace of phenolsulphonephthalein elimination. These figures distinctly show that retention of waste products is occurring.

Four days later, the patient had three convulsions and was stuporous, the blood figures were as follows: Cholesterol, 640 mg, nonprotein nitrogen, 111, urea nitrogen, 67, uric acid, 7, creatinin, 14.1, sugar, 0.144 per cent, carbon dioxide combining power 14 volumes, indican, ++++. The following day, the patient's general condition was much improved (note the last rise in the cholesterinemia) and remained so for about ten days, but during the interval the following figures were obtained: Cholesterol, 497 mg (a considerable fall), nonprotein nitrogen, 112, urea nitrogen, 63, uric acid, 5.5, creatinin, 11.1, sugar, 0.18 per cent, indican, ++++, and no elimination of phenolsulphonephthalein.

At this stage of his illness, the patient again became worse, convulsions of increasing severity and duration, with dulness and apathy set in, and the following figures were obtained: Cholesterol, 339 mg, nonprotein nitrogen, 125, urea nitrogen, 59, uric acid, 12.5, creatinin, 11.6, sugar, 0.120 per cent, carbon dioxide combining power, 24 volumes, indican, ++++. Five days later, with convulsions, stupor and restlessness continuing, the following figures were obtained: Cholesterol, 338 mg, nonprotein nitrogen, 117, urea nitrogen, 72, uric acid, 4.2, creatinin, 12.3, sugar, 0.153 per cent, carbon dioxide combining power, 29.6 volumes (treatment directed to combat the acidosis), indican, ++++. The following day convulsions became very frequent, stupor deepened into coma, and the patient died. Blood obtained before death gave the following figures: Cholesterol, 249 mg, nonprotein nitrogen, 144, urea nitrogen, 100, uric acid, 12.5, creatinin, 13.4, sugar, 0.20 per cent, carbon dioxide combining power, 24 volumes, indican, ++++.

Here, then, is a case in which the cholesterinemia fell gradually from 797 to 249 mg in the course of six weeks, while the nonprotein nitrogen constituents of the blood steadily increased in amount. It is the fall in the measure of cholesterinemia that is the significant feature in estimating the prognosis in any given case.

It has long been my belief that the lipoids of the blood play a rôle analogous to an antitoxin, and are intimately associated in immunologic processes. The lipoids seem to act as a protection to the animal organism, and are known to counteract certain poisonous substances. Recent literature abounds in substantiation of this belief.

PROGNOSTIC VALUE OF CHOLESTERINEMIA IN CHRONIC NEPHRITIS

Case	Sex	Age	Blood Pressure	Urine Analysis			Blood Analysis, Mg per 100 Cc							Remarks
				Phenol phthal ein	Albu min	Microscopical	Choles terol, Gm per 1 000	Non protein Nitro gen	Urea N	Creat inin	Uric Acid	Sugar, per Cent	Ind- ica- tion	
1	M	66	220		+	H and G casts	2.05		55	1.0	2.7	0.132		General condition not good
2	F	60			+	H and G casts	1.73	125	100	13.4	5.5	0.129	10.0	Patient died in coma in three days
3	F	59	180		+	H and G casts	1.65		17.5	1.5	1.4	0.09		Vomiting, stupor, coma, death
4	M	50	170	79	+	H and G casts	2.34	110	58	3.5	5.0	0.136	42.0	General condition good
5	F	61	210		+	H and G casts	1.43	41	16	1.1	1.0	0.146	48.5	Threatened uremia
6	M	52	150		+	None	2.02		16	1.5	2.7	0.106		Early death in coma
7	M	55	170		+	H and G casts	2.93		35	1.3		0.112	31.0	Death from cerebral hemorrhage
8	M	67	185		+	H and G casts	1.77		31	2.5	2.3	0.12	48.0	Coma, uremia
9	M	50	200		+	H and G casts		141	85	6.0	10.0	0.152	15.0	Coma, death
10	M	27			+	None	1.85	250	150	18.7	10.0	0.2	14.0	Uremic coma and death
11	M	35	240		+	H and G casts	0.97	55	165	18.0	10.0	0.24		Uremia
					+	H and G casts	1.45		25	3.5	5.0	0.2		No pending uremia
					+	H and G casts	1.00		19	1.9	3.6	0.1		Coma, death
					+	H and G casts	3.49		15	1.5		0.06		General condition good
					+	H and G casts	3.00				2.6		55.0	General condition good
					+	H and G casts	2.42							Nausea, vomiting
					+	H and G casts	1.80							No change
					+	H and G casts	1.10		19	1.5				Stupor, drowsy
					+	H and G casts	7.97							Muscular twitchings coma, death
12	M	23	194	tr	+	H and G casts	5.02	77	24	5.3	2.3	0.124	18.0	No evidence of impending uremia
				tr	+	H and G casts	6.40	106	55	13.6	7.0	0.172	14.0	Some languor
					+	H and G casts	4.97	111	67	14.1	7.0	0.114		Three convulsions
					+	H and G casts	4.18	112	63	11.1	5.5	0.18		Ocasional convulsions
					+	H and G casts	3.39	100	67	12.8	8.3	0.135		Convulsions, apathy
			170		+	H and G casts	3.38	125	59	11.6	12.5	0.12	24.0	Drowsy, dulness, convulsions
					+	H and G casts		117	72	12.5	4.2	0.113	29.6	Stupor, convulsions
					+	H and G casts	2.49	144	100	13.4	12.5	0.20	24.0	Convulsions, coma, death

"Cholesterol is no fortuitous component of the organism" <sup>2</sup> Barbary <sup>3</sup> believes that cholesterol stimulates the production of antibodies. In his hospital at Nice, where during twenty months he cared for 767 wounded and 797 sick soldiers, he had a strikingly low mortality—four deaths among the wounded and nine deaths among the sick. He attributes the good results obtained to the general use of the following mixture: Cholesterin, 0.2 gm., camphor, 0.5 gm., strychnin sulphate, 0.0005 gm., in 50 c.c. of olive oil washed in alcohol.

Urra <sup>4</sup> found that cholesterol neutralizes toxins. He found that a hypercholesterinemia is to be found in all severe toxic processes at the time the toxemia is being overcome, referring especially to nephritis and typhoid fever. Several years ago <sup>5</sup> I showed that a definite hypocholesterinemia exists during the fever period of typhoid, a slow return to normal as the fever approaches normal, and a decided hypercholesterinemia during convalescence.

Manfredi <sup>6</sup> has shown that the addition of cholesterol to cultures of typhoid bacilli (even in amounts less than are found in the blood stream) checked the growth of the organism. Other organisms, such as the colon bacillus, the streptococcus of erysipelas and puerperal fever, the staphylococcus, diphtheria and cholera bacilli, were also checked in their growth. The hypercholesterinemia of pregnancy is acknowledged to be a fact, and as the result of the study of more than one thousand cases, I believe a relative hypercholesterinemia is to be found in puerperal fever.

Goormaghtigh <sup>7</sup> has shown that the suprarenal supplies cholesterol to the blood stream in infectious diseases, and in grave infections, terminating fatally, the reserve of cholesterol was demonstrated to be exhausted.

Morato and Villanueva <sup>8</sup> have shown that the injection of cholesterol with typhoid vaccine hastened the production of antibodies and agglutinins. They cite researches of others who have shown the benefit following the administration of cholesterol in those conditions in which a hypocholesterinemia is found.

Cholesterol has been shown to be antitoxic to the venom of a viper and a cobra. It has been shown to neutralize the toxin of sausage

<sup>2</sup> Editorial, J. A. M. A. **62** 620 (Feb. 21) 1914.

<sup>3</sup> Barbary. Cholesterin and Camphor to Mobilize and Reinforce the Natural Defensive Powers, *Bull. de l'Acad. de med., Par.* **76** 221.

<sup>4</sup> Urra. The Defensive Lipoids. *Semana med.* **24** 506.

<sup>5</sup> Hennes. Cholesterinemia, *Proc. New York Pathol. Soc.* **13** No. 7.

<sup>6</sup> Manfredi. Effect of Cholesterol in Culture Medium on Development of Germs, *Riforma med., Naples* **33** 849.

<sup>7</sup> Goormaghtigh. The Functioning of the Suprarenal Capsules in Infections, *Arch. med., Belges* **70** 697.

<sup>8</sup> Morato and Villanueva. Cholesterol a Factor in Immunity and in the Production of Agglutinins, *Med. Ibera Madrid* **9** No. 107.

poisoning and to attenuate tuberculin, and it has been used in the treatment of tuberculosis and various anemias

These references to the literature have been presented in justification of my belief that cholesterol plays some protective rôle in the animal organism. The prognostic value of the measure of cholesterinemia in chronic nephritis becomes of greater interest and importance because of these facts. The researches of the past years seem to justify a conclusion I came to eight years ago. "Cholesterinemia seems to be of prognostic importance in some diseases and an indicator of their severity. Researches in cholesterinemia are still in their infancy. Much work is necessary before the many problems this lipid presents in its relation to the organism, both under normal and pathologic conditions, can be solved. We have yet to determine more exactly, above all, its origin and destiny, the physiology and pathology of the quantitative variations in the blood, the significance of these variations and the possible rôle cholesterol can play in therapy"<sup>5</sup> Many of these problems have since been solved.

I wish to acknowledge my indebtedness to Mr. A. Bernhard, in charge of the chemical laboratory of the Lenox Hill Hospital, for the chemical examinations of the blood in the cases reported.

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# CLINICAL OBSERVATIONS ON UNUSUAL MECHANISMS OF THE AURICULAR PACEMAKER

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In the clinical records from the electrocardiographic laboratory of the Massachusetts General Hospital are some examples of unusual mechanisms of the auricular pacemaker worthy of discussion

## 1 AN UNUSUAL TYPE OF AURICULAR PAROXYSMAL TACHYCARDIA

Simple paroxysmal tachycardia is defined as a tachycardia of sudden onset and sudden offset, with a striking regularity of rate, and arising from an abnormal point or ectopic focus in the auricles or ventricles. Such, indeed, is the usual occurrence. Some irritable spot in the heart takes away the initiative or impulse formation from the pacemaker or sino-auricular node in the right auricle. Whipping up the heart on its own account, it carries on this dominant rhythm till exhausted when once more the normal pacemaker resumes its work after a short pause.

Theoretically, an abnormal pacemaker like the ectopic focus is beyond nervous control and ceases its activity spontaneously. Sometimes, one finds clinically, however, that nervous influences may readily induce a paroxysmal tachycardia, and other nerve stimuli, such as pressure on the vagus nerve or eyeball, may stop it. The mechanism is not easy to explain in a number of such cases, but the important exciting factor is certainly extracardiac.

In paroxysmal tachycardia the electrocardiogram usually confirms the idea that the new pacemaker is "ectopic" by presenting a very abnormally shaped P or auricular wave. Normally, the P wave is upright in the electrocardiogram, but in paroxysmal tachycardia of the usual auricular type, the P wave is apt to be inverted.

Rarely one finds a case of auricular paroxysmal tachycardia in which the ordinary definition fails to hold. Such an instance is shown in Figures 1 and 2. Short paroxysms of tachycardia occur in which there is a markedly rapid, but not immediate, increase in the heart rate to the maximum, and a tendency to offset of the same type. Moreover, the shape of the P wave is normal or close to normal. The explanation of such a paroxysm of tachycardia is that it results from unusual nervous stimulation of the normal pacemaker or of a point in close proximity to the normal pacemaker in the sino-auricular node.

The measurements of the intervals between the heart beats in the case described here normally were about 0.77 second. The measure-

ments between the heart beats at the beginning of the paroxysm in Figure 2 are as follows 0.651 second (the beat preceding the paroxysm), 0.407, 0.425, 0.384, 0.323, 0.316, 0.325, 0.308, 0.327, 0.317, 0.336, 0.316. The measurements of the intervals at the end of the paroxysm in Figure 2 were 0.323, 0.318, 0.310, 0.370, 0.830 (the beat after the paroxysm). At the height of the paroxysm, also shown in Figure 2, the intervals were 0.316 second, 0.323, 0.310, 0.326. The normal rate of the heart was 78 per minute. The rate of the tachycardia at its maximum was about 188 per minute.

CASE 1—R. M., male, aged 21 years, was born in Italy. He was a worker in a jewelry shop.

*Family History*—One sister was demented.

*Past History*—The patient has had no serious illness in the past. He never has had rheumatic fever, chorea or tonsillitis. He always has been nervous.

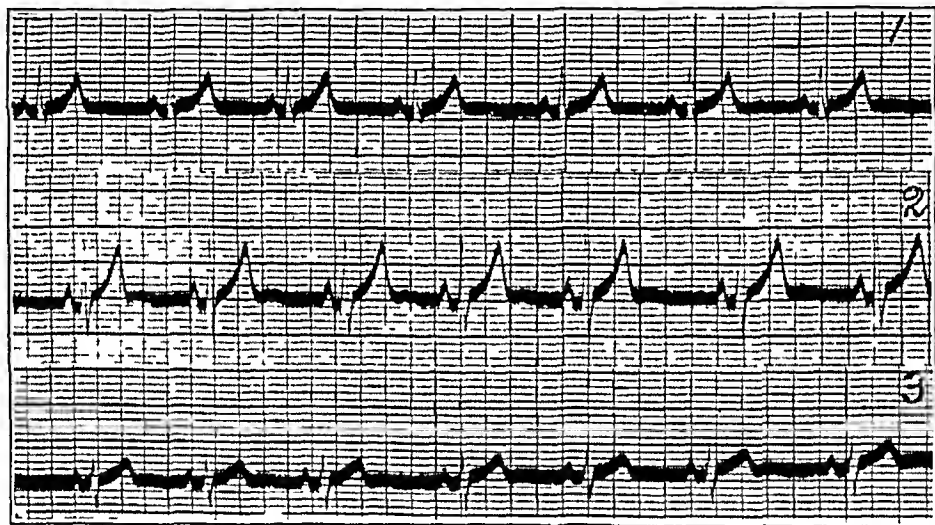


Fig 1—Electrocardiogram of R. M. (Case 1), showing normal rhythm in all three leads. T wave in Lead 2 is very high. Some respiratory arrhythmia is present. Lead 1 above, Lead 2 in middle and Lead 3 below. Abscissa = 0.2 sec., ordinate =  $10^{-1}$  volt.

*Present Illness*—His present trouble, "palpitation," began seven years ago with a rapid heart beat in short paroxysms with choking sensation. He feels better now and then, and sometimes has no spells for months.

*Examination*—This was entirely negative, except for frequent short paroxysms of tachycardia. The Wassermann reaction was negative. Roentgenogram of the heart was normal. Basal metabolism estimation was normal.

This patient has been under observation for five years, being first seen in October, 1914. He has constantly shown the same phenomenon, but has remained in good health otherwise; he has not had to stop work. Unfortunately, the paroxysms were too brief for experimentation, rarely lasting more than ten seconds each. While being examined



under particularly exciting conditions, paroxysms occurred frequently, his heart at times beating more paroxysmally than normally

Somewhat comparable is the voluntary acceleration of the rate of the pacemaker as seen in published electrocardiograms<sup>1</sup> In the voluntary acceleration cases, however, the increase in rate is less rapid Carter and Wedd<sup>2</sup> have reported a case of paroxysmal tachycardia characterized by unusual control of the fast rhythm The focus of the ectopic rhythm was apparently near the pacemaker and could be abolished at will, but the rate of the paroxysm was quite regular at about

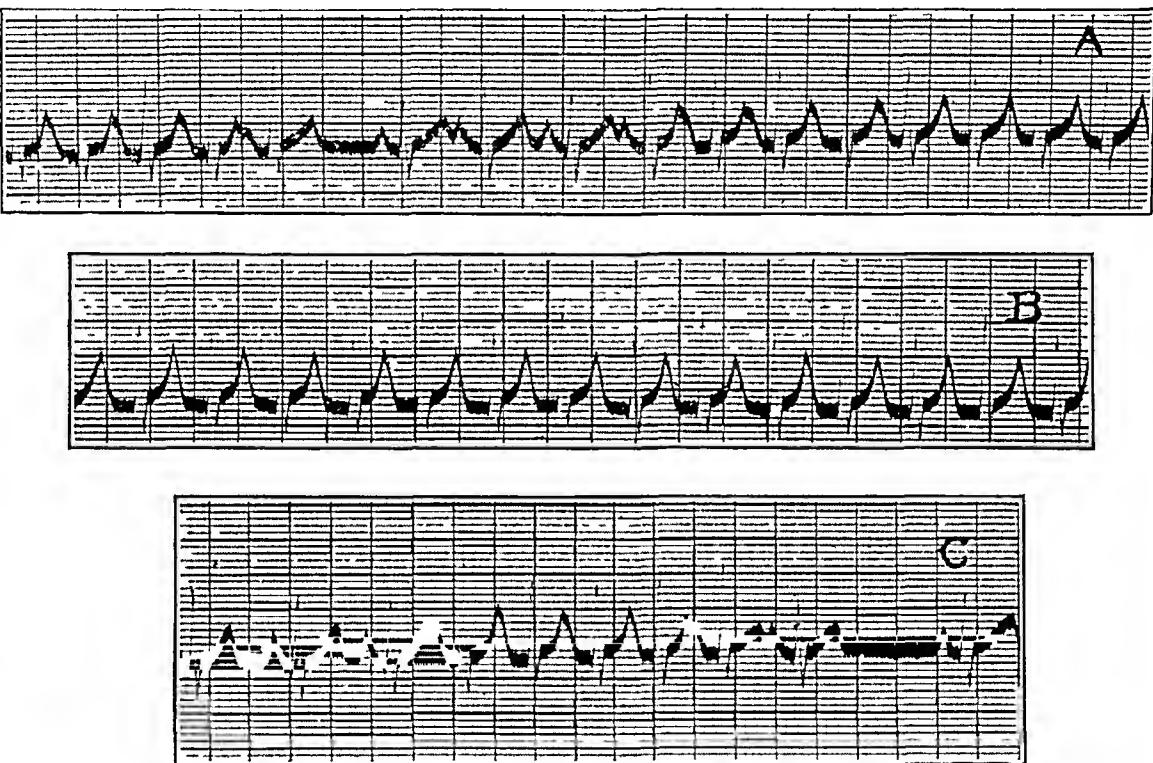


Fig 2—Electrocardiograms showing paroxysms of tachycardia of R M (Case 1) All are of Lead 2 In the upper record (A) the offset of one paroxysm and the onset of another are shown In the middle record (B) a paroxysm appears at its height In the lower record (C) a short complete paroxysm is photographed Observe in this lower record particularly the gradual onset and gradual offset

200 (196 to 204) and was not under accelerator control In the abrupt transition from an abnormal rate to normal, this case differed from the one reported here

Recently, Prof Giovanni Galli,<sup>3</sup> of Rome, called attention to the nomotopic (nomos, custom, topos, place) type of paroxysmal tachy-

<sup>1</sup> Favill, J, and White, P D Heart 6 175, 1917

<sup>2</sup> Carter, E P, and Wedd, A M Arch Int Med 22 571 (Nov) 1918

<sup>3</sup> Galli, G Arch d mal du coeur, 12 289, 1919

cardia He writes on the manner of termination and onset of the attacks in nomotopic paroxysmal tachycardia, and gives the following points in favor of the possible diagnosis of sino-auricular paroxysmal tachycardia

1 The sino-auricular node is composed of irritable muscle tissue Why should it not be the source, then, occasionally of paroxysmal tachycardia?

2 Vagal excitation may influence paroxysmal tachycardia

3 Atropin may induce paroxysmal tachycardia (Galli mentions a case in which the heart rate jumped from 90 to 200 after administering atropin)

4 Emotion may start a paroxysm

5 The Valsalva experiment may sometimes stop a paroxysm

6 There was a progressive increase ("crescendo") and decrease ("diminuendo") in the paroxysm in some of the tracings he obtained Thus, there was a "parabolic development" with termination by "lysis"

7 Sometimes, at the onset of a "normal sino-auricular tachycardia" there may be a brusque change in heart rate

8 The P wave in the electrocardiogram may appear of normal or nearly normal shape

9 Experimental stimulation of the extracardiac nerves, for example, the right stellate ganglia, may induce a marked tachycardia

10 Nomotopic paroxysmal tachycardia seems to have a better prognosis than the usual paroxysmal tachycardia, as one might expect

## 2 VARIATION IN POSITION OF THE PACEMAKER AS SHOWN BY THE SHAPE OF THE P WAVE, THE LENGTH OF THE PR INTERVAL AND THE HEART RATE

Lewis, Meakins and White<sup>4</sup> showed experimentally that the pacemaker in the sino-auricular node of a dog's heart varies its position with vagal stimulation, moving to or near the distal or tail end of the node Its movement downward toward the ventricle tends to shorten the auriculoventricular interval or P-R interval as expressed electrocardiographically, but since ordinarily vagal stimulation depresses the auriculoventricular junctional tissues as well as the head of the sino-auricular node, the P-R interval may be actually lengthened rather than shortened

Einthoven<sup>5</sup> observed the change in the shape of the P wave with prolongation of the P-R interval in vagal stimulation Goddard<sup>6</sup> noted that the size and shape of the P wave may vary at different times in the same curve, and an inverted P in one record may appear upright in a later tracing, and vice versa

4 Phil Tr Roy Soc London **205** 375 (Series B) 1914

5 Einthoven, W Arch f d ges Physiol **122** 517 1908

6 Goddard, C H Arch Int Med **16** 633 (Oct) 1915

Wilson<sup>7</sup> has discussed the mechanism of the pacemaker within the sinus node or within its immediate neighborhood, as well as its migration from the sinus to the *a-v* node, and has published electrocardiograms illustrating the migration resulting from respiratory influences

According to theory, with the migration of the pacemaker from the head toward the tail of the sino-auricular node and to the *a-v* node, the P wave becomes flattened and finally inverted, the P-R interval becomes shorter, providing there is little or no simultaneous vagal effect on the *a-v* junctional tissue, and the heart rate drops

Two electrocardiograms obtained at the Massachusetts General Hospital illustrate such a variation in position of the pacemaker by tendency to negativity of the P or auricular deflection and by a shortening of the P-R interval, and in one case by the decrease in the heart rate. The first instance, the type usually seen, was the result of vagal pressure in a man aged 33 years, who was seriously ill with chronic nephritis, and cardiac enlargement and weakness. The electrocardiogram, Lead 2, is shown in Figure 3. Here, right vagal pressure was applied at first in

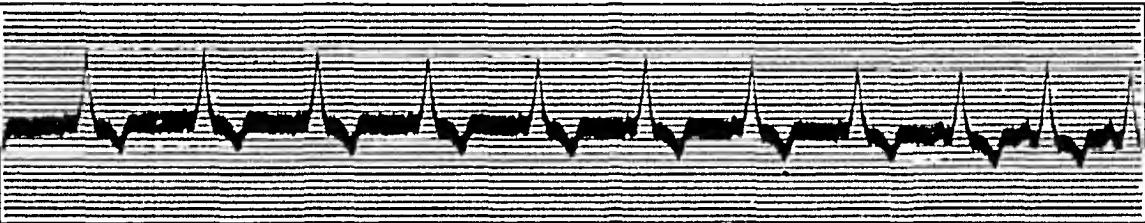


Fig 3—Electrocardiogram (Lead 2) of E M showing the effect of right vagal pressure on the auricular pacemaker. The dislocation of the pacemaker toward the ventricle is indicated by the change from normal in the shape of the P wave, the shorter P-R interval and the slower heart rate. The T wave is markedly inverted.

the record and then released. The P wave at first flattened, returns to a normal upright shape. The P-R interval at first measuring 0.099 and 0.098 second, becomes at the end of the record 0.146 and 0.144 second. The heart rate at first 83, becomes 108. Of interest in this case is the fact that the sino-auricular node has been definitely depressed by the vagal stimulation, but the *a-v* conduction has not been slowed.

The second record is that obtained spontaneously from an elderly lady (Mrs M.) with arteriosclerosis and an arrhythmia consisting of ventricular premature contractions. In the course of one minute P waves of different shapes were found. The electrocardiogram, Lead 2, is shown in Figure 4. Apparently the pacemaker is moving about rap-

<sup>7</sup> Wilson, F. N. Arch Int Med 16:86 (July) 1915, Am J Dis Child 10:376 (Nov) 1915.

idly in the node, in the first record alternating between a high and low position, the P-R intervals alternating as well as the change in shape. The first low P carries with it an interval of 0.124 second, the next P, a much higher one, a P-R interval of 0.152 second. The following P-R intervals continue to alternate: 0.124, 0.155, 0.125, 0.155 second. The interauricular intervals are 0.989, 0.977, 0.988, 0.995 and 1.018 seconds. Finally, the inverted P waves in the second record (Fig. 4) have very short P-R intervals of 0.099, 0.103, 0.101 second. It will be noticed that a premature ventricular beat interrupts the rhythm and is followed by a deeply inverted P wave (retrograde). It is probable that the inverted P wave arises from the region at the lower end of the *s-a* node, at the junction of the auricle with the *a-v* node, or between the two, as indicated by shape and by P-R interval. The interval between the

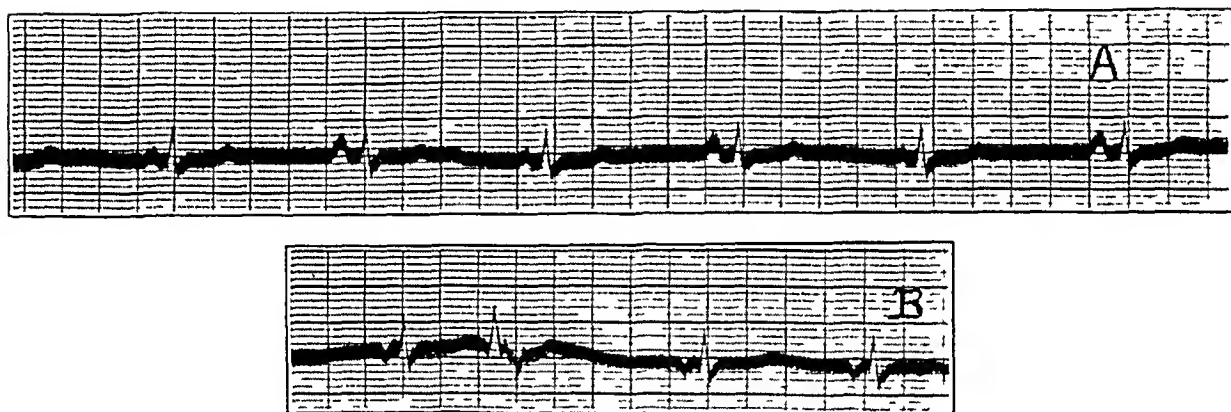


Fig. 4—Electrocardiograms (Lead 2) of Mrs. M. (Case 3), indicating in the upper record (A) alternation in the position of the pacemaker as shown by the alternating change in shape of the P wave and by the alternating length of the P-R interval. In the lower record (B) the auricular impulse is arising from a point still nearer the ventricle as shown by the inversion of the P wave and by the short P-R interval. A ventricular premature beat with retrograde impulse to the auricles interrupts the rhythm in the lower record (B).

two rhythmic inverted auricular waves in this strip is 0.866 second, which is less than that between the more normal auricular complexes in the upper record. The explanation of this is not clear, unless, perhaps, the premature contraction is disturbing the rhythm.

These records were made from a private patient during the war by Miss Mabel Hopkins, and there was no opportunity to investigate the condition further. The patient had not had digitalis. Of particular interest in this case is the alternation in the site of the pacemaker.

### 3. SUDDEN HALVING OF THE AURICULAR RATE ("SINO AURICULAR HEART BLOCK") AFTER EXERCISE

CASE 2—W, a young man, aged 24 years, a renowned athlete in college football two years before, showed a sudden halving of the pulse rate coming

on one minute after a fast run of about one-quarter of a mile. Electrocardiograms of this occurrence showed the onset of the so-called sino-auricular heart block, the sino-auricular pacemaker changing abruptly from a rate of 88.2 per minute to one of 44.8 per minute, rising shortly to 53.6 (Fig 5). The rate remains slow. The man was healthy.

The sino auricular block in this athlete was undoubtedly due to marked vagal action following exercise. It is possible that this phenomenon occurs occasionally in athletes.

The more usual form of sino-auricular block, generally a digitalis effect due to the depression of the sino-auricular pacemaker, is shown in Figure 6. This is an electrocardiogram of a woman, aged 33 years, with heart apparently normal, but with a cough of obscure origin. She was seen in the outpatient department of the Massachusetts General Hospital during the war. She had not had digitalis.

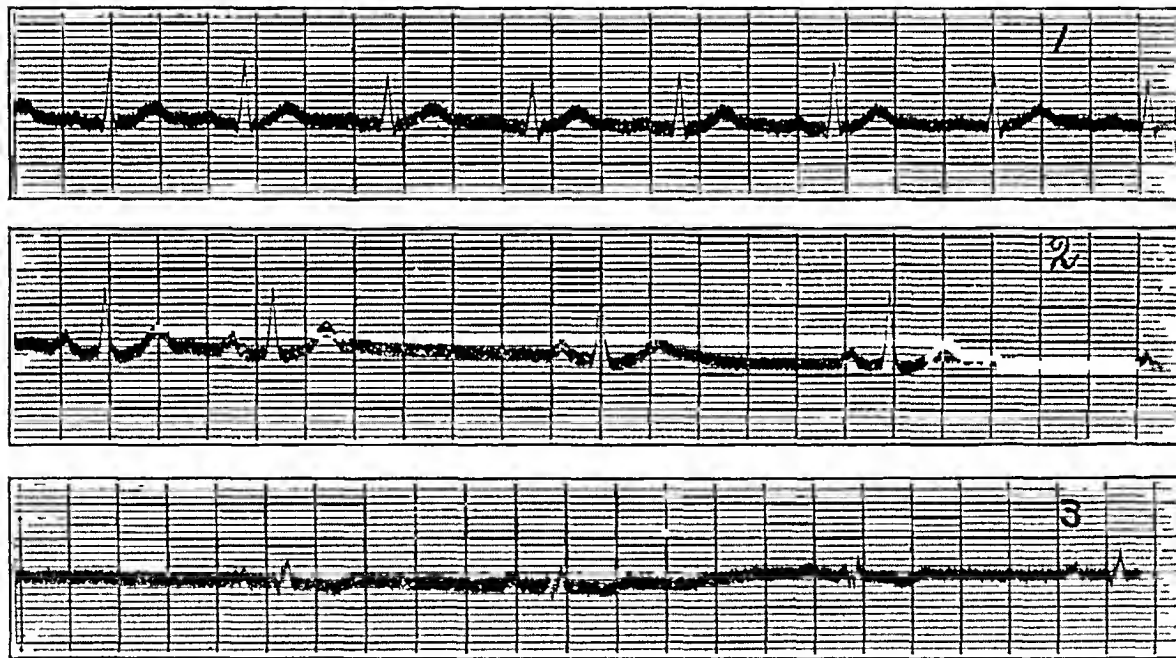


Fig 5—Electrocardiograms showing Leads 1, 2 and 3 of P. D. W. taken in order immediately after exercise. In the middle record occurs the sudden halving of the auricular rate (sino-auricular heart block) from 88.2 to 44.8 per minute.

Levine,<sup>8</sup> in 1916, reported four cases of sino-auricular block seen at the Peter Bent Brigham Hospital. Three of these patients had had digitalis. He collected fourteen cases from the literature, four of which are very doubtful, because in two no graphic records were made, and in the two others only radial tracings were taken. The arrhythmia due

<sup>8</sup> Levine, S. A. Arch. Int. Med. 17: 153 (Jan.) 1916.

to sino-auricular block was apparently the result of digitalis in seven cases, but in five others there was no statement as to whether or not digitalis had been given.

White,<sup>9</sup> in 1916, reported three cases seen at the Massachusetts General Hospital, in which all evidence of auricular action was temporarily abolished by digitalis, that is, auricular standstill or complete sino-auricular block was present. In another case, reported by White,<sup>10</sup> there was evidence of sinus bradycardia due to digitalis, in which instance the auricular rate was 41 and the ventricular rate 82 at times.

Thomas Lewis, in his "Clinical Electrocardiography," published two electrocardiograms of sino-auricular block, one from a case of mitral stenosis and one from a case of exophthalmic goiter. In 1913<sup>11</sup> he reported a case of unusual bradycardia in which there was no trace of auricular activity in the electrocardiogram or jugular tracing. No statement as to digitalis administration was made in this case.

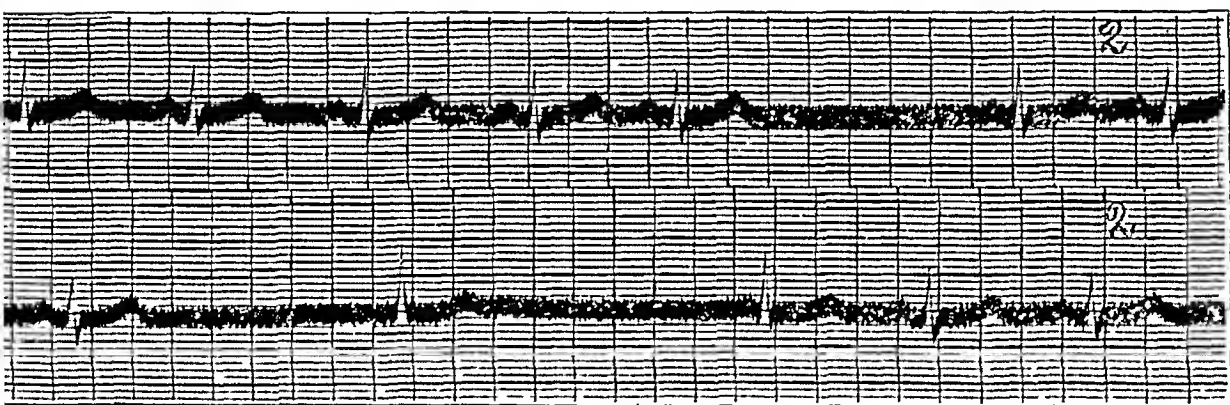


Fig 6—Electrocardiogram (Lead 2) of E. L. showing sino-auricular heart block, not resulting from the action of digitalis.

Brown<sup>12</sup> recently described a case of sino-atrial heart block in a child, 11 years of age, with acute arthritis. Here there had been no digitalis administration. Atropin abolished the block.

In spite of the rarity of its publication, it is probable that sino-auricular block occurs more frequently than we have been led to suspect.<sup>13</sup>

9 White, P. D. Boston M. & S. J. **175** 233 (Aug. 17) 1916.

10 White, P. D. Arch. Int. Med. **18** 244 (Aug.) 1916.

11 Lewis, T. Quart. J. Med. **6** 221, 1913.

12 Brown, N. W. Arch. Int. Med. **24** 458 (Oct.) 1919.

13 Another case of sino-auricular block has been seen at the Massachusetts General Hospital since this article was written. This makes the seventh seen at this hospital during five years, three with complete and four with partial sino-auricular block. The patient was a woman, aged 56 years, with cardiosclerosis with slight cardiac failure, she had not had digitalis.

## SUMMARY

Three clinical examples of unusual mechanism of the auricular pacemaker are reported

1 Paroxysmal tachycardia arising in or very near the sino-auricular node and not showing an absolutely abrupt onset or offset

2 Migration of the pacemaker in the sino-auricular node, two foci alternating action in one case

3 Sudden halving of the auricular rate (sino-auricular block) after exercise

# FETID SPIRILLAR BRONCHITIS AND PULMONARY GANGRENE

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LIÈGE, BELGIUM

Castellani<sup>1</sup> noted in soldiers of the Italian Army the not infrequent occurrence of an affection of the respiratory tract which he had described previously at Ceylon, and of which he had recognized the specific agent. This affection he had termed *bronchospirochetosis*. It appears under two aspects. A form of short duration, lasting from one to three weeks, and running its course after the fashion of an acute bronchitis, with fairly high temperature during the early days, a form with a prolonged course simulating a chronic bronchopneumonia of long duration, several years in most cases, but sometimes taking on a malignant character, with irregular fever, hemoptysis, progressive enfeeblement and emaciation, and lethal termination.

The specific parasite is a spirillum, *Spirochaeta bronchialis*, very polymorphous, from 4 to 30 microns long, 0.2 to 0.6 micron in thickness, presenting from two to eight undulations and sometimes more, the extremities of variable shape, often pointed and without flagella.

H. Violle<sup>2</sup> published an article on an affection of the respiratory tract characterized by bloody expectoration, which he termed hemorrhagic bronchitis. The secretion of the bronchial mucosa is abundant, nearly a quarter of a liter in twenty-four hours. It is tenacious, stringy, viscous, homogeneous, of a bright rosy color, resembling gooseberry juice. It is sufficient, says Violle, to have seen it once to escape the danger of confounding it with tuberculous hemoptysis. On examination of the chest, the results vary: sometimes nothing, sometimes a slight enfeeblement of the vesicular murmur, sometimes signs of a simple bronchitis with or without areas of pulmonary congestion, sometimes, finally, very clear cut signs of chronic bronchitis and emphysema. The general condition is good, often, indeed, very good, there is no fever, the expectoration contains spirochaetes in great abundance. The organisms show an extraordinary polymorphism, and this variation in their shape and dimensions is one of their special characteristics.

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1 Castellani, A. Note sur la "Broncho-spirochaetose" et les bronchites mycosiques, affections simulant quelquefois la tuberculose pulmonaire, Presse med 25 377, 1917.

2 Violle, H. La spirochaetose bronchopulmonaire (bronchite sanglante), Rev gén de clin et de therap 32 144, 1918.



This affection, for which the author suggests the name of *hemorrhagic bronchitis with spirochetes*, justifies, generally a favorable prognosis. After ten or fifteen days the expectoration ceases to be mucohemorrhagic, and complete recovery follows fairly rapidly. Nevertheless, relapses, as in the acute form described by Castellani, are surprisingly frequent, and the disease may take on a chronic course with varying periods of exacerbation.

During the war I described, in collaboration with Dr P. Spehl,<sup>3</sup> an acute affection of the respiratory tract, the clinical aspect of which is that of a bronchitis or a bronchopneumonia with the special characteristic that the breath of the patient and his expectoration becomes fetid rather early in the course of the development of the disease, the etiologic agent appears to be a spirillum. This malady, so far as we know, has not been observed elsewhere. It would seem to us to be distinguished from the bronchospirochetosis of Castellani and from the bronchitis due to the spirillum described in France by H. Violle.

In my opinion the disease observed by us is not of tropical origin. It is probable that it must be met with in times of peace among the civil population of countries of temperate climate. It has seemed to me that it might be interesting to bring our observations to the attention of the English speaking medical public.

CASE 1—Dec A, aged 25, infantryman, fell ill, April 23, 1917, and experienced suddenly, a sensation of general malaise, with headache, pains in the extremities and loins. Cough soon followed, with frothy, whitish expectoration, and a few days later laryngitis. On entry into the hospital, April 29, the patient complained of headache and of general pains. Temperature from 38.6 to 39.4 C, pulse accelerated, from 104 to 112, respiration, quiet, cough, paroxysmal, fatiguing and accompanied by mucopurulent expectoration, whitish gray, of a very fetid odor. There was laryngitis, the voice was hoarse, the naso-pharynx was intact. On examination of the thorax the resonance was normal. Auscultation showed a few sibilant râles, especially at the right base. The general condition was satisfactory.

In the succeeding days the bronchitis increased, the cough became more frequent as well as the expectoration, the fetor of which increased. May 4, the percussion note was diminished at the right base, and auscultation revealed, chiefly at this point, numerous subcrepitant râles. The temperature fell below 37 C, May 9 (seventeenth day) and did not rise again until May 20 (twenty-eighth day) when, without apparent cause, there was a slight congestive attack at the right base, at the end of two days the temperature fell again to normal. The local trouble was slow in improving. The râles diminished after May 11 but did not disappear until the middle of June. Laryngitis persisted until the end of the same month.

After May 5, microscopic examination of the sputum revealed for about three weeks the presence of numerous spirilla. Their number together with the fetor of the expectoration diminished after May 20. They disappeared May 25, but the breath of the patient remained fetid until May 29.

<sup>3</sup> Nolf, P., and Spehl, P. La bronchite fétide à spirilles, Arch. méd. Belges 71 1, 1918.

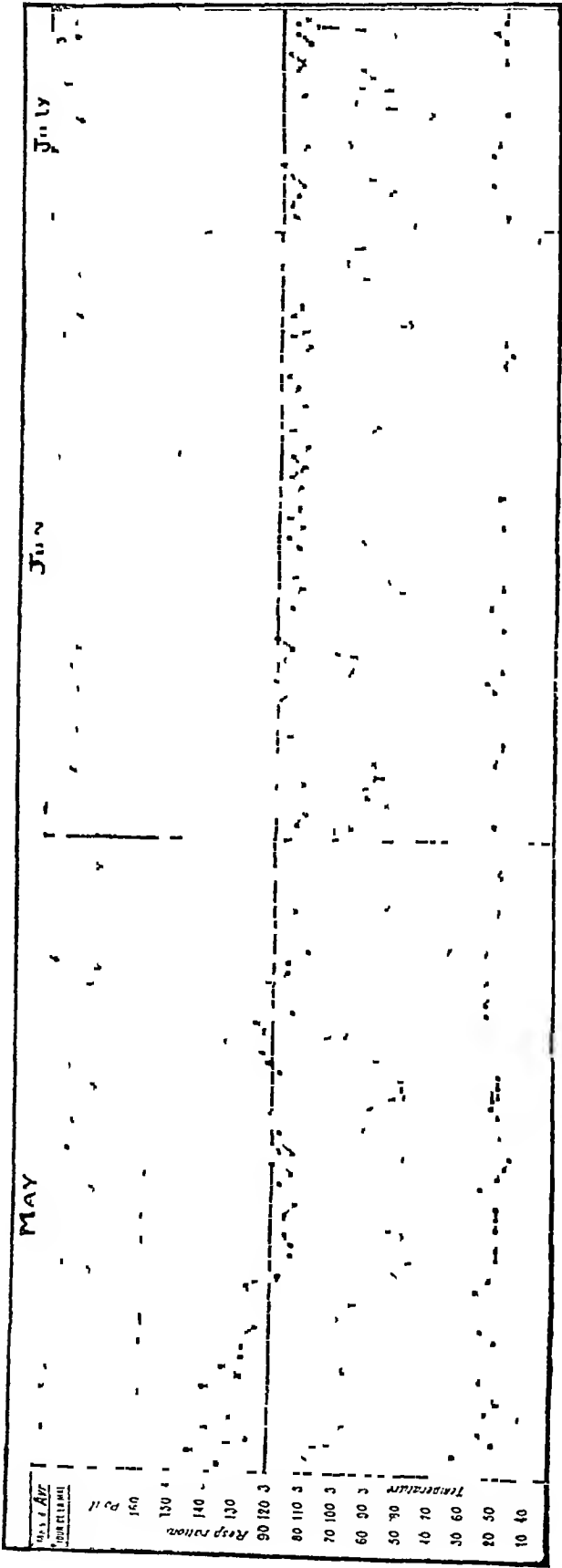


Figure 1

Treatment consisted of warm, moist packs for the chest, with application of tincture of iodine in enemas of creosote and in intravenous injections of novarsan, repeated from May 5 to the end of the month, every five days, in a dose of 45 cg. The amelioration of the general condition became apparent after the first injection and much more so after the second. The local lesions were not influenced so rapidly. Later, heliotherapy appeared to accelerate convalescence.

For the laryngitis insufflations of sodium benzoate were relatively inefficacious.

CASE 2—Theun, aged 27, infantryman, suffering from a simple cold, complained on June 29, 1917, of general malaise, thoracic pain, headache and a little difficulty in swallowing. He coughed, expectorated moderately and showed a little fever.

Entering the hospital July 6, on the first clinical examination there was noted a rather elevated temperature (from 38 to 39.5 C), a pulse of 100 and slight increase in the size of the spleen which reached the costal border on deep inspiration.

The arterial pressure was normal (155/80, Pachon). Examination of the thorax was negative. Chemical examination of the urine, including Diazo reaction and cultures, blood culture, Widal reaction, search for malarial parasites, were negative. There was a slight leukopenia (from 4,400 to 4,800 leukocytes), the blood formula (lymphocytes 19, mononuclears, medium 5, large 1, intermediate 1, polymorphonuclear neutrophils 13, eosinophils 1) was normal.

Up to July 17 (nineteenth day) the fever oscillated continually between 38 and 39.5 C. The patient raised, without particular auscultatory signs, a moderate fetid bronchial expectoration which did not contain tubercle bacilli but spirilla in considerable numbers. From this time on a series of injections of novarsan (from 30 to 60 cg) was begun, at intervals of four days, and as adjuvant medication, there was prescribed a daily enema of creosote. After six injections, representing only about 195 gm of novarsan, the spirilla disappeared from the expectoration.

However, this treatment remained without action on the general condition of the patient, which became aggravated, or on the temperature, which continued to oscillate between 38.5 and 39.8 C.

August 20 (fifty-second day) a laryngitis appeared. The fetid expectoration increased, medium moist râles appeared at both bases. The pulse increased to 125, the respiration to 30. Intravenous injections of peptone, digitalin and strychnin were added to the previous medication. Despite all, the condition of the patient became worse, and death followed September 9 (seventy-third day).

At the necropsy there was edema of both lungs, but no tubercles. At the hilum of the right lung were four enlarged glands. In the pulmonary tissue were some miliary abscesses which do not contain spirilla, tubercle bacilli or giant cells. The spleen was enlarged. The heart, liver, kidneys, intestines were normal.

CASE 3—Dav J, aged 26, detached for service at a hospital, fell ill suddenly August 20. On this date he showed a general malaise, depression, chills, pain in the chest, dyspnea, cough and expectoration.

On entrance (August 23) the patient was much prostrated, the body was covered with cold sweat, the face and extremities were cyanotic. The temperature was 39.5 C, the pulse and respiration were accelerated, the cough was frequent, expectoration was scanty, mucopurulent, colorless, odorless and aerated. The tongue was moist and white, there was complete anorexia. The urine was deeply colored and showed traces of glucose and albumin.

The upper respiratory tract was normal, percussion of the lungs showed nothing suspicious. On auscultation, disseminated sibilant râles could be heard. Hot packs were applied to the chest and this was painted with tincture of iodine. During the following days, the fever remained elevated, pros-

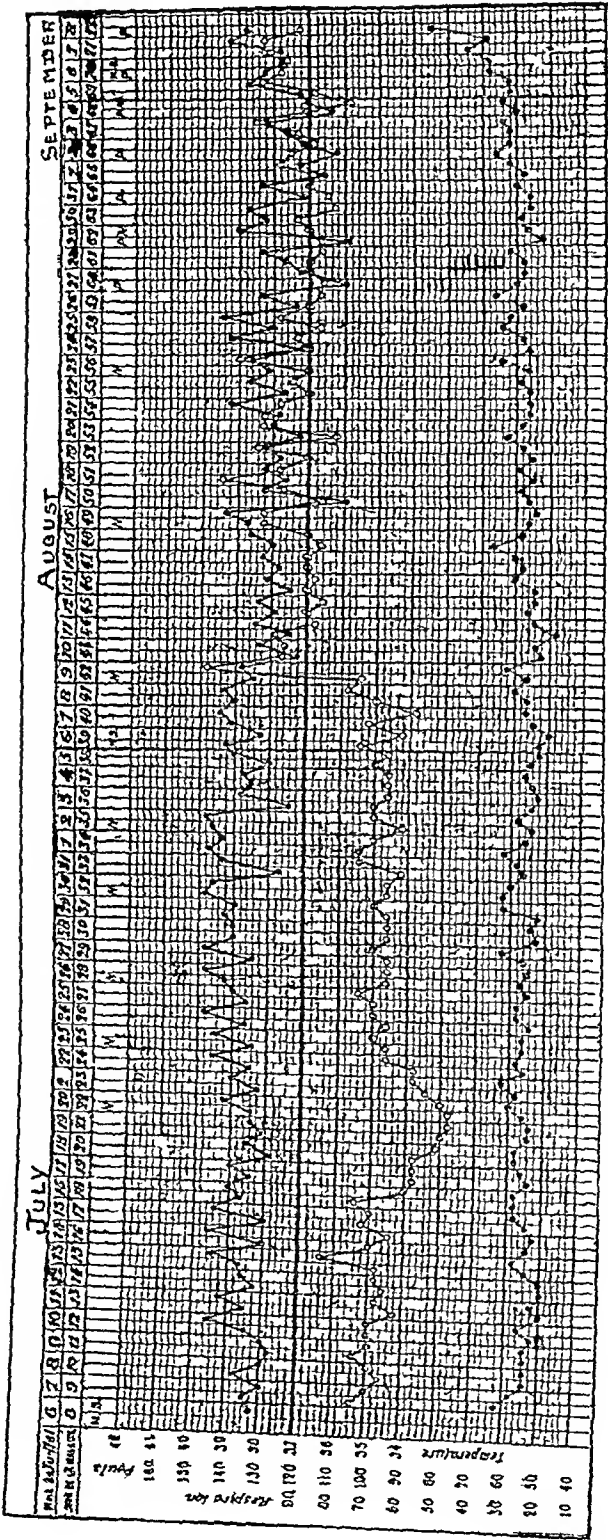


Figure 2

tration and dyspnea persisted, the sibilant râles diminished greatly, but the expectoration increased, became greenish in color and of a foul odor. Microscopic examination made August 26 revealed spirilla in moderate numbers, but no tubercle bacilli. A series of intravenous injections of novarsan was begun (60 cg on August 26 and 29 and on September 5 and 12) and peptone was given intravenously as an adjuvant (1 gm on August 31 and September 2, 4, 6, 8, 10, 12 and 17).

The spirilla disappeared after September 3, but the expectoration remained fetid up to the middle of the month. Gradually, the pulmonary symptoms receded, the general condition improved, and recovery was complete at the beginning of October.

CASE 4—Pier M., aged 24, infantryman, was taken ill Jan 13, 1918, with general fatigue, left pleurodynia, severe chill, fever and abundant sweating. This was followed by cough and rusty expectoration. He entered the hospital, January 16, with symptoms of congestion at the base of the left lung. The temperature was 39.5 C, the pulse and respiration were accelerated. Moist warm packs for the chest were prescribed.

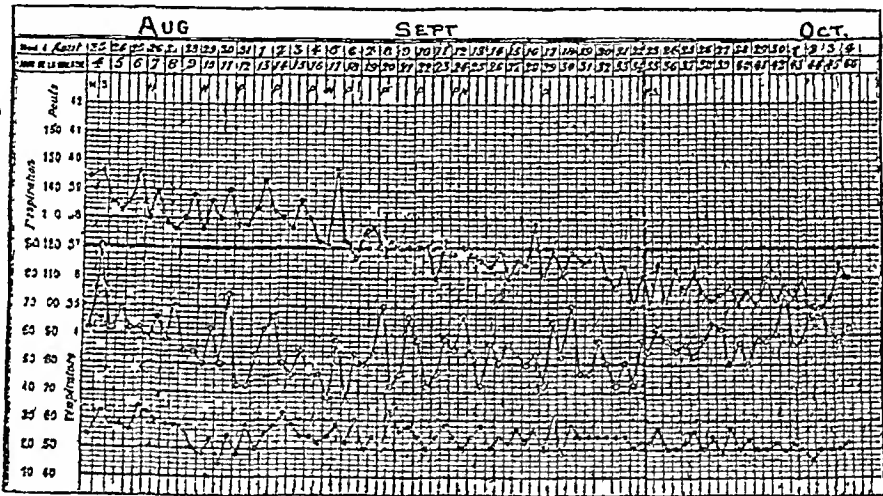


Figure 3

Two days afterward, moist râles were heard at both bases, in the right scapular region there were crepitant râles and slight dulness.

The breath became fetid. The expectoration was mucopurulent and of a greenish color. A daily enema of creosote, 2 gm to 100 cc, and an intravenous injection of 30 cg of novarsan were prescribed. Examination of the blood revealed 15,500 leukocytes per cmm, and a leukocyte formula of 9 lymphocytes, 5 medium sized mononuclears, 5 large, 2 intermediate forms, and 79 polymorphonuclear neutrophils. The sputum showed occasional spirilla in addition to an abundant and varied bacterial flora. Injections of novarsan (45 to 60 cg, repeated every five days) and intravenous injections of peptone were continued to March 18. The temperature fell irregularly to February 6, rising several days afterward and remaining between 37 and 38 C. The auscultatory signs (moist râles, fugitive areas of blowing breathing corresponding to areas of bronchopneumonia, with areas of dulness or slight loss of resonance) continued up to February 7. After this date there remained only signs of bronchitis. The general condition improved progressively, keeping pace with the condition in the chest. A blood examination made February 11 showed 85 per cent hemoglobin (Gowers), 5,460,000 red blood cells and 7,800 leukocytes. Under the influence of pulmonary radiotherapy and heliotherapy, the patient seemed to be entering on convalescence.

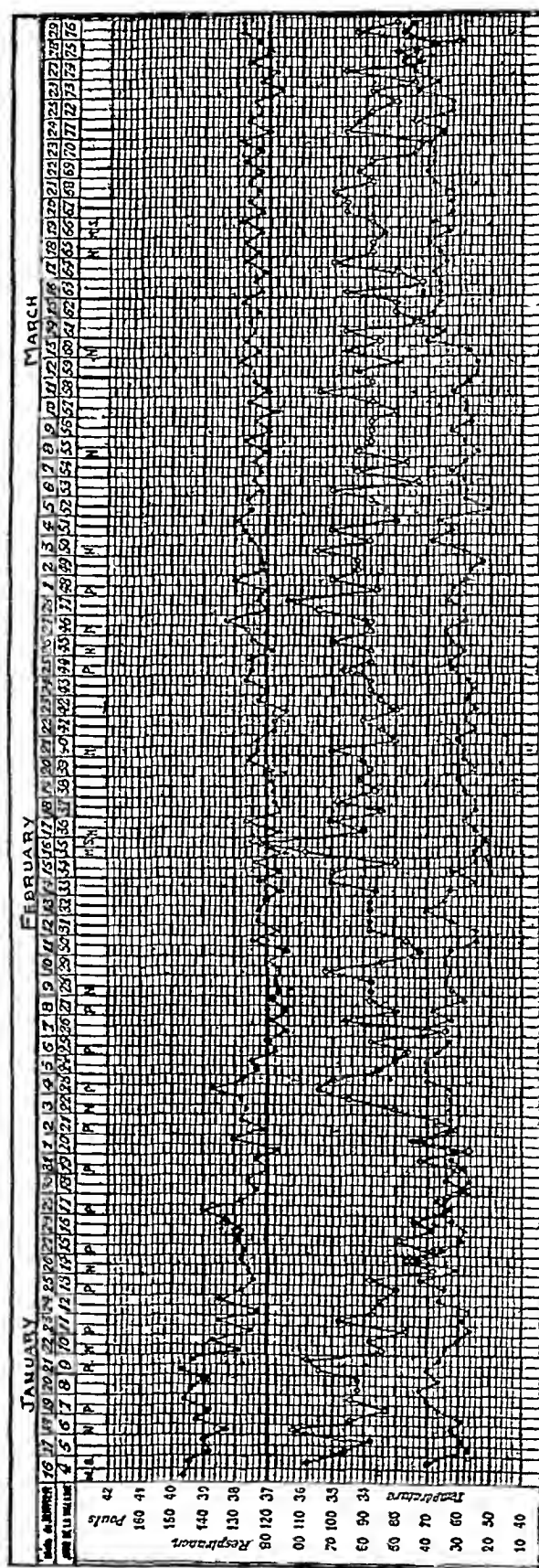


Figure 4

The expectoration remained fetid to the middle of February (sixth injection of novarsan), the spirilla increased to the same time, and then diminished, disappearing with the fetor of the breath about March 8 (tenth injection of novarsan)

**CASE 5 — Deh** F, aged 27 years, infantryman, subject to winter bronchitis, was seized suddenly Feb 5, 1918, with several chills, some associated with actual chattering of the teeth. There was headache, nose bleed, nausea and vomiting on five occasions. February 6 and 7 he had colic and three or four liquid stools, slight cough, no expectoration.

The patient entered the hospital February 13. Temperature, 38 to 39.5 C, pulse, 100, respiration, 30, nothing abnormal on physical examination. February 14 blood cultures were sterile, no agglutination with dysentery bacillus, typhoid or paratyphoid, but the spleen was palpable. February 15 cultures of the urine and Diazo reaction were negative. On that day, however, the patient began to raise reddish and then rusty expectoration, and examination of the chest revealed dullness at the right base with rough respiration. A few moist râles were heard in this area February 17. The expectoration remained

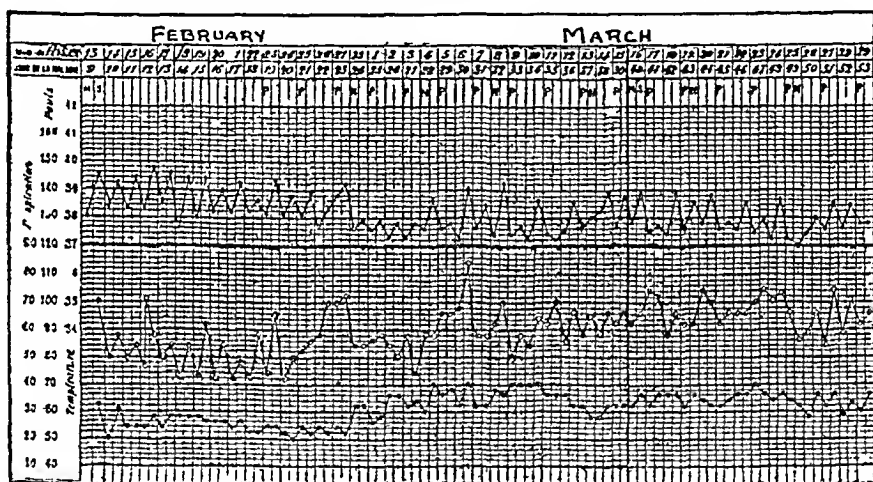


Figure 5

moderate, inodorous, at times mucopurulent, but always contained more or less blood. The temperature remained elevated. New agglutinative tests were made, likewise fresh cultures from the blood and urine, these threw no light on the diagnosis. Because of the intoxicated and prostrated condition of the patient, repeated intravenous injections of peptone were carried out every other day.

February 27, while the condition was still unimproved, the patient began to expectorate a brownish sputum with a pronounced odor of lactic acid. Microscopically, the presence of numerous spirilla (Figs 7 and 8) was revealed. February 28, along with peptone and wet packs for the chest, a series of intravenous injections of novarsan (30, 45, then 60 cg) was carried out every five days. In addition, injections of creosote were given, as well as heliotherapy and cod liver oil. During March the pulmonary symptoms continued to remain very slight, the expectoration remained red or brown and still contained numerous spirilla. March 16. After March 23 (fifth injection of novarsan) it became paler, more like an ordinary mucous expectoration and contained fewer pathogenic bacteria. The general condition improved slightly. The temperature did not become definitely normal until after March 12, that is until after nine injections of neoarsphenamin. The patient received a tenth injection March 18 and left the hospital entirely convalescent June 21, 1918. Frequent search for the tubercle bacilli in the expectoration was always negative.

CASE 6—Van P H, aged 27, artilleryman, was seized March 12, 1918, with a stitch in the left side and dyspnea. There was fever, cough, abundant expectoration and epistaxis. March 16 the expectoration became fetid. March 20 the patient entered the hospital. Examination of the chest at this time showed slight dulness at the right base, sonorous and sibilant râles disseminated throughout the two lungs, and medium moist râles in the outer part of the left chest. Physical examination was otherwise negative. The temperature ranged from 37.5 to 39 C. The pulse was accelerated (96), respiration was a little rapid (24). The sputum, examined March 21, was rather purulent, greenish, moderately fetid and contained neither tubercle bacilli nor spirilla. Wet packs were applied to the chest and creosote was administered daily by enema.

March 22 a fresh examination of sputum showed some spirilla. Arsenical treatment was begun. Thereafter the spirilla became more abundant and the fetor of the expectoration increased sharply. At the end of March the disease was still at its height and the general condition remained serious. March 30

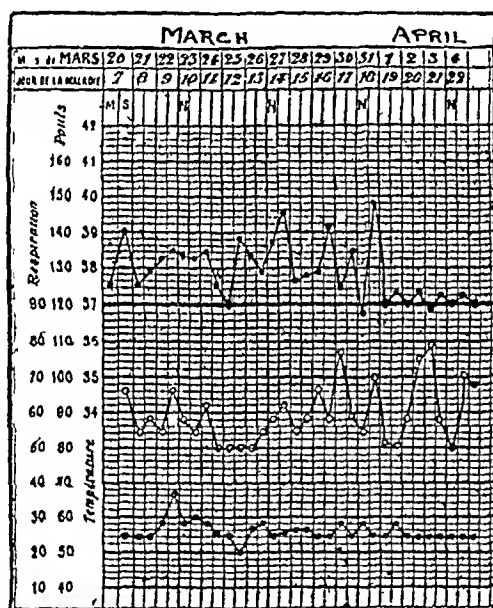


Figure 6

the expectoration contained no more spirilla. March 31, 60 cg of novarsenobenzol was given intravenously. After this last injection the general condition of the patient improved, the fever disappeared. For twenty-four hours the patient expectorated more freely. The odor had nearly disappeared from the sputum, there were no spirilla. The soldier left the hospital entirely well April 22, 1918.

In examining the sputum collected in sterile petri dishes after careful rinsing of the mouth, we found in the first four cases and in the sixth, a spirillum, which, although rather variable in its size, presented morphologically an appearance which permitted of its recognition with a little experience. It stained very badly with the basic coloring matters ordinarily used in bacteriology. In order to bring it out, one must have recourse to some mordant. We used the method of Fontana, which gives excellent impregnations when the preparation is spread in



a sufficiently thin layer, or a procedure described by one of us,<sup>4</sup> which consists of the use of formol and chromic acid as mordants, staining by formalized violet and reinforcing by Lugol's solution. After this treatment the spirilla are of a brownish-black color (Fontana) or of a bluish-black (Spehl) on the colorless background of the preparation. Their dimensions are variable. Their length varies from 8 to 12 microns, their thickness is about that of Vincent's spirillum, it is a little greater in the preparations stained by Fontana's method. The extremities are tapering and appear not to carry flagella, at least we have never seen them in our preparations. The convolutions are short, sometimes regular, generally irregular, some being much less well marked than their neighbors, which results, perhaps, from the circum-

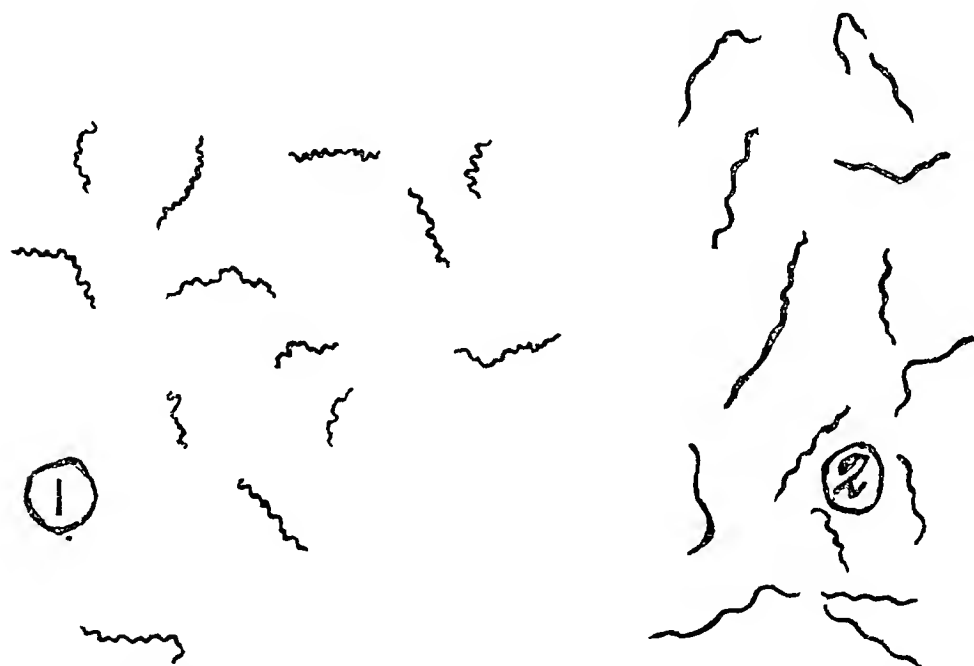


Fig 7—1 Spirilla of fetid bronchitis found in the expectoration of all our patients (Drawing made with camera lucida,  $\times 750$ ) 2 Spirilla of Vincent (Drawing made with camera lucida,  $\times 750$ )

stance that the parasite generally takes on a sinuous form, each one of sinuosities including a greater or less number of convolutions. The usual number of convolutions is from seven to eight for the adult forms. Exceptionally, we have counted as many as ten and eleven. What seems to us especially characteristic from the point of view of form is the coincidence of elbows or undulations of large size and of short, crowded convolutions, which gives to the spirillum a particularly tortuous character (Fig 7). The accompanying figure drawn with the camera lucida, reproduced fairly faithfully the appearance of the preparation.

<sup>4</sup> Spehl, P. Procédé de coloration des spirilles par le violet-formole, *Compt rend Soc de biol* **81** 305, 1918

In examining these two figures, one may see morphologic differences which distinguish clearly the spirillum of fetid bronchitis from the spirillum of Vincent

So far as we know few spirochetes take this aspect. With some experience it is easy to differentiate the micro-organism which we have found in our cases of bronchitis from the two known spirilla of the buccal cavity, such as the spirillum of Vincent (*Spirillum refringens*) and *Spirochaeta dentium*). We do not, then, wholly share the opinion of Castellani and Violle, each of whom insists on the extreme polymorphism of the spirochetes which they have described. Indeed, we have succeeded in finding, alongside of these forms, which we regard as characteristic, spirillum of aberrant form, sometimes in great numbers.

Our first observation was made prior to these two publications. It dates back to April, 1917. Between April, 1917, and July, 1918, we observed ten other cases among about 5,000 patients who passed through our first line hospital during this period. In our eleven patients there was also bronchitis, or more frequently bronchopneumonia, as in those of Castellani and Violle, but the clinical appearance and evolution differed at several points from the affection described by those authors.

In nine of our eleven cases the disease was primary. It seized the men in good health, and generally had a sudden onset, characterized by one or more chilly sensations or shaking chills. The patient suffers from general malaise, headache, pains in the extremities and loins. The spleen was palpable in two instances. The cough generally produced pain in the chest without an actual stitch. In one case there was epistaxis, scanty but repeated. In several cases the pulmonary symptoms were very slight in the earlier days of the disease, which appeared rather as a general affection than as a malady of the respiratory tract. Even after the symptoms related to the respiratory tract have developed further and taken a prominent place in the picture, there may, at the outset, be nothing characteristic, the local signs being those of an ordinary bronchitis and the expectoration mucopurulent, frothy, without special morphologic or bacteriologic characteristics. But there is one characteristic common to all the cases, namely, that the disease never shows the least spontaneous tendency to recovery.

The fever, generally irregular, is at the outset elevated, or tends progressively to rise, the general condition becomes aggravated, the patient loses strength, is feeble, out of breath on the least effort, while the face and extremities assume a more or less marked cyanosis. In the chest the signs of bronchitis, indefinite at first, become clearer and more extensive, in the posterior parts of the lungs zones of dulness or diminished resonance develop, localized commonly at the bases, the

expectoration becomes more and more abundant, it is slightly aerated, purulent rather than mucopurulent, of a greenish yellow color, and — an important sign — it becomes fetid while the breath takes on a repulsive odor. This fetor of the breath and expectoration has been manifested in all of our patients. In the grave cases it existed at the outset and had a cadaveric character. With the spasms of cough it spread to some distance, and distressed the patient's companions in the ward at a distance of several meters. Sometimes the air of the whole room was poisoned.

In the milder cases the fetor was not evident in the early days of the disease, or was too slight to attract attention. It was only after several days that it was perceived by the hospital personnel, or sometimes by the patient himself. But, as has been said, it always appeared at some period in the evolution of the malady, generally precociously. This characteristic is all the more notable in that it is not pointed out by Castellani or Violle.

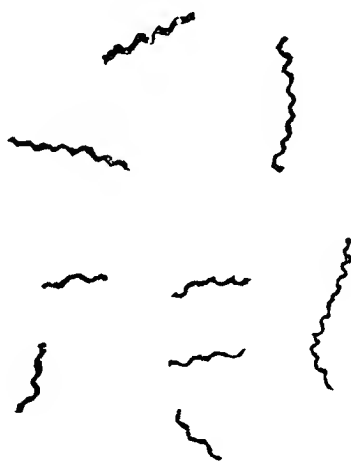


Fig 8—Spirilla in sputum in Case 5 (Camera lucida drawing,  $\times 750$ )

The expectoration of our patients is distinguished further from the bronchial secretions of patients observed by Violle. It was hemorrhagic in only one case. In this case it had the characters of glary, viscous masses with a homogeneous rose violet color. Later, it took on a brownish hue. In another patient, the expectoration was rusty in the first days of the disease, but became rapidly mucopurulent. Apart from these two cases the bronchial secretion of our patients always had the color and consistency described in the brief résumé of the history of six persons attacked by the primary form of the disease. Thus, in Case 5, which is, by the way, the only instance of expectoration regularly bloody in the early days of the disease, we found, for the greater part, forms a little different from those which have been described, generally shorter, less tortuous, a little thicker, and a little less tapering at the extremities (Fig 8).

Alongside of these there were, however, fewer spirilla having the characteristics of those which we found in all our other patients. It is difficult to express a definite opinion as to the question whether the micro-organism represented in Figure 8 is different from that shown in Figure 7 (1).

In one of the patients, where the affection was secondary (Case 7) and in whose expectoration the spirilla were particularly abundant, there were, alongside of the ordinary forms, a certain number of spirilla which, from their appearance, recall the spirillum of Vincent. In this case, which was one of particular gravity, the expectoration was extremely abundant and of a repulsive fetor. Possibly, the bronchial lumina had been invaded secondarily by the micro-organisms of the mouth, which in this very sick man, may have found in the bronchial secretions an excellent culture medium.

An interesting point is the greater or less abundance of spirilla in the expectoration. In certain patients they are very abundant. They may be found, so to speak, in every field of the microscope, sometimes several in each field, even in very thinly spread preparations. But it is not always thus. In other instances the micro-organisms are much rarer. One must sometimes examine a large number of fields before finding one. In a general way, one may say that the gravity of the affection is in direct proportion to the number of the spirilla. In the fatal cases they are as abundant in the bronchial mucus as is the spirillum of Vincent in the detritus which covers the ulceration of the disease tonsil.

It has seemed to us that the more numerous they were, the more fetid was the breath and the expectoration, and it was because in our first patient this fetor was very striking and the number of spirilla great, that we thought immediately of seeking a relation between the one and the other, and recognized the possibility of the pathogenic rôle of the spirillum. On the other hand, when, under the influence of treatment, the disease tends toward recovery, improvement goes hand in hand with the diminution of the spirilla in the secretion, a diminution which becomes evident even when the general characters of the expectoration, excepting the odor, have as yet shown no change.

In summary we found in our six patients with a primary fetid bronchitis a spirillum which seems to us to be the same in all cases, except for the circumstance that in Case 5 it was associated with a second form.

From a clinical point of view, the affection is sufficiently characteristic to permit its recognition after several days of observation at least. That which distinguishes it, as has been said above, is the high remittent fever, which has no tendency to fall spontaneously, despite a severe regime (rest in bed, liquid food, wet packs to the thorax, expect-

torants or balsamics) progressive loss of strength, dyspnea on the slightest effort, more or less well marked cyanosis and the peculiar character of the breath and expectoration. All of our last cases have been recognized clinically before confirmation from the laboratory. As a matter of fact, we hold that the only possible confirmation is the habitual presence in the sputum of a spirillum with the staining characteristics and the form described.

When one examines carefully the bronchial expectoration of patients affected with acute or chronic inflammation of the bronchi or of the pulmonary tissue, one may discover occasional spirilla, but this is rather an accidental event. The micro-organisms are rare, and have not, from the standpoint of their shape, the characters that we have found constantly in all of our cases. The question which arises is as to what is the etiology of this affection and how it spreads. Is it a malady analogous to whooping cough or measles, whose parasite exists only in those who are affected with or in the period of incubation of the disease, or must it be placed alongside of pneumonia whose micro-organism is to be found in the upper respiratory tract of healthy subjects. Our two cases of secondary fetid bronchitis speak in favor of the second alternative. The first case was that of a man, who, having a gastric ulcer, was obliged to undergo a gastro-enterostomy because of persistent hemorrhage at a time when his resistance was low. Immediately after the operation, there was fever, attributable to a pneumonia at both bases, which from the outset was characterized by a fetid breath and mucopurulent expectoration rich in spirilla. This man had been in the hospital for four weeks, in a ward where no similar case had been treated previously. The affection pursued its course to a fatal issue in twelve days.

The second case was that of a soldier who had been gravely intoxicated by dichlorethylsulphid. The bronchopneumonia produced by the poison took on an infectious character on the fourth day. Little by little, the expectoration became fetid. This phenomenon led to a microscopic examination of the sputum which revealed the presence of very numerous spirilla, but, curiously enough, the spirilla particularly abundant in these two extremely grave and fatal cases, after a short course, were the same in their staining affinities, their dimensions and their form as those found in the cases of primary bronchitis. We are, therefore, led to conclude that the upper respiratory tract of these two men normal up to that time, harbored the specific spirillum, and as there is little reason to believe that they were in a period of incubation, since the first had been cared for at the hospital for more than four weeks, we are rather led to conclude that the spirillum of fetid bronchitis may exist as a saprophyte in wholly healthy individuals. In like manner, we may add, that although our patients suffering from the

primary affection were never isolated, and although they lived for considerable periods in the common wards, we have never observed an instance of contagion. The affection is, however, relatively rare, since we have had only eight cases,<sup>5</sup> as against eighty-three of pneumonia and bronchopneumonia treated during the same period.

The history follows of two cases of secondary bronchitis.

CASE 7—J O R E, aged 29, in the auxiliary service, for a year has suffered from intermittent gastric disturbance. September 8, 1917, he was seized by vomiting, which continued during the following days and was preceded by pyrosis. Hematemesis occurred on the evening of September 20 and necessitated his entering the hospital on the twenty-first.

On examination, a diagnosis of gastric ulcer was made, and the patient was treated by suitable diet, calcium chlorid and several intramuscular injections of peptone. His general condition being sufficiently improved, he underwent an operation for gastro-enterostomy (ether narcosis) October 25. With the exception of several attacks of vomiting the results of the operation were good.

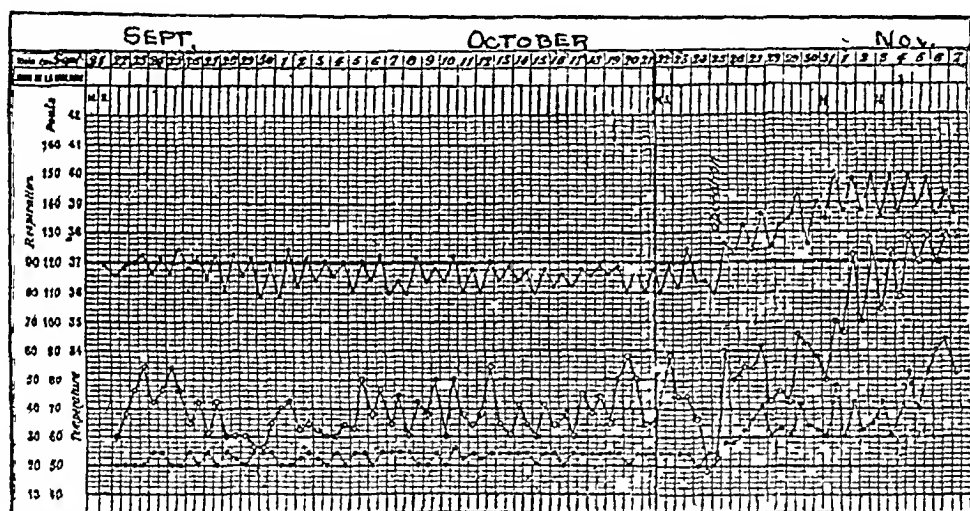


Figure 9

October 27 the patient began to expectorate a little mucus. The cough brought on vomiting. October 28 and 29 the vomiting ceased, but expectoration became mucopurulent and increased in quantity. October 30 the expectoration began to give forth a slightly disagreeable odor, but became clearly fetid on the following day, and was of a frankly purulent character. A microscopic examination made October 31 revealed numerous spirilla. The patient was immediately transferred to a medical ward and received an intravenous injection of 45 cg of novarsenobenzol. Examination of the thorax revealed dulness at the bases of the lungs, especially the left. In places there was pectoriloquy and blowing breathing. Dyspnea was marked and prostration striking. Warm moist packs were applied to the chest. November 1 the fetor increased and this increase continued until his death. November 1 the fetor persisted. Digitalin was administered. November 3 a few fine râles appeared in the middle of the left lung in addition to the râles of bronchitis, and another dose of novarsan was administered. November 4 and 5, the general condition improved and intravenous injections of peptone were given.

<sup>5</sup> In April and May, 1918, we had occasion to care for three new cases, and to bring the patients to recovery by intravenous injections of novarsan.

November 6, the symptoms became aggravated. The spirilla were always very abundant, the fetor of the breath was evident in the ward, dyspnea was intense, the patient was given oxygen through a nasal tube, and camphorated oil, strychnin and tartar emetic. November 7 there was bilious vomiting. The patient died at 5 p. m.

At necropsy the lungs showed a generalized edema, patchy bronchopneumonia and miliary abscesses, *in the pus of which the pathogenic spirilla were found*.

CASE 8—Baud R, aged 25, infantryman, intoxicated by dichloroethylsulphid during the night of November 12 to 13, entered the hospital on the thirteenth suffering from burns of the face, eyes, scrotum and a general bronchitis. There was a little cyanosis of the extremities, but respiration was quiet and the pulse was not accelerated. Despite hot, wet packs to the thorax, the application of tincture of iodine and Dover's powder, the patient's condition became worse, the fever and pulse increased.

November 15 the respiration was blowing at both bases and accompanied by moist râles and a diminished resonance. Small doses of digitalin and ipecac

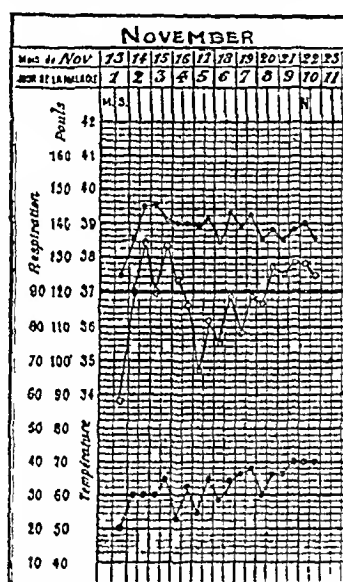


Figure 10

were given. The local signs, the exhaustion and cyanosis persisted, the expectoration became more abundant and took on a purulent character (November 20). Iodotannic syrup and creosote enemas were added to the treatment. November 21, the patient became definitely dyspneic. He was given oxygen continuously, strychnin and camphorated oil. November 22 the expectoration became fetid. Immediately, the patient received a potion of tartar emetic and an intravenous injection of 60 cg of novarsenobenzol. Microscopic examination of the sputum showed many spirilla. November 23, his condition was desperate, there was pronounced fetor and numerous moist râles were audible in the chest. Death ensued in the morning.

At necropsy the lungs were generally edematous and congested and there were areas of disseminated bronchopneumonia. The glands of the hilum were enlarged.

If there were still doubt concerning the pathogenic rôle of the spirillum, it would be removed by the curative influence of the organic preparations of an arsenic base. This action is indeed not always

shown at the outset. Treatment must be long to control the disease definitely. If a series of intravenous injections of novarsenobenzol is made, in doses of from 45 to 60 cg., five or six days apart, a change in the clinical picture, rather slow in its development, may usually be made out. The condition, which, up to that time, has grown progressively worse, shows little by little, signs of an improvement, which, interestingly, affect first the elements characteristic of the affection. On the one hand, the fetor of the breath and the expectoration becomes less. On the other hand, there is a diminution in number, or even disappearance of the spirilla under the microscope. During this early period of arsenical treatment, the fever may remain tolerably high, and the local signs in the pulmonary apparatus are little influenced. It may even be that with the continuation of the arsenic treatment, the disappearance of the spirilla is brought about without amelioration of the general or local condition. This occurred in Case 2, which ended fatally. We have observed that the arsenical treatment acts better and more quickly the earlier it is begun.

This circumstance may be explained when one considers that the spirillum is far from being the only micro-organism to be found in the sputum which contains a particularly varied and abundant bacterial flora. The micro-organisms of which this consists probably add their injurious action to that of the spirillum. At the necropsy done in Case 2, both lungs were found dotted with miliary abscesses, of which the pus did not contain spirilla (tubercle bacilli were also absent), although the expectoration of the patient contained many before the beginning of arsenical treatment. It would appear that the lesions produced by the spirilla are severe, and that, invaded by the micro-organisms of secondary infection, they present little tendency to heal. This, perhaps, is the most distinctive character of the affection described in this article. Even after our patients had been rendered apyretic, and after their expectoration from being purulent had become mucous and free from spirilla, they continued to cough, and auscultation revealed signs of an attenuated but persistent bronchitis. We have had to have recourse to the combined action of balsamics, exposure to sun, and respiratory gymnastics definitely to overcome these sequels which always show an extreme obstinacy.

In certain cases we have added to intravenous injections of novarsenobenzol, peptone, administered intravenously every two days. It has seemed to us that this combination was more effective than treatment by arsenic alone (see especially Case 3).

We have termed the malady described in this article "fetid spirillar bronchitis," although, in reality, certain forms have from the outset taken on the clinical characters of a bronchopneumonia, and although at necropsy in the fatal cases there have been found either areas of



bronchopneumonia or pulmonary abscesses. The appellation "bronchitis" seemed to us to be more suitable because, at least in the primary form of the affection, the signs in the respiratory tract were very vague in the early days of the disease, and were those of an acute bronchitis. The examination of the sputum having proved that in addition to a spirillar infection there is added a considerable number of other micro-organisms, it is impossible to settle the question as to whether the extension of the bronchial inflammation to the pulmonary parenchyma is attributable to the spirochete or to the organisms of secondary infection. In the early days of the disease, when it is primary, the fetor may be absent or slight, and the spirilla very scanty in the expectoration. It may even be impossible to make them out at that time. Although the disease is not malignant, it is to be differentiated, however, from an acute bronchitis by a sudden onset with high fever, general phenomena, and especially a complete lack of tendency toward spontaneous recovery. After from several days to several weeks the patient loses his strength, becomes emaciated, his bronchitis merges into bronchopneumonia, the spirilla tend to become more abundant in the expectoration, while the fetor of the breath also becomes aggravated. All the patients observed by us were soldiers in the Belgian Army in the field, who had not lived in tropical countries, and had never been in contact with colonial troops.

For this reason, and for the others mentioned above, we have differentiated the affection from the two maladies analogous and yet distinct one from another, described, one by Castellani,<sup>1</sup> and the other by Violle,<sup>2</sup> both of which appear to originate in warm climates.

If, as we thought, the affection is autochthonous, it remains to be explained why we have had occasion to see a considerable number during the course of a year when, so far as we know, no disease of this sort had previously been described in temperate regions.

The most probable explanation appears to be the following. If the case is benign and remains benign (this eventuality we have not observed, but our observations do not permit us to exclude it), if it ends in recovery spontaneously or favored by treatment, there is considerable likelihood that it may be regarded as an acute catarrh of the upper respiratory tract. If, on the contrary, the malady becomes aggravated and lethal in its course, it will impress the uninformed physician as being an acute bronchopneumonia which, at a given moment, is complicated by pulmonary gangrene.

As a matter of fact, the observations at necropsy in our fatal cases do not at first glance plead in favor of this point of view. One observes in the examination of the lungs postmortem, the presence of diffuse congestion and edema, areas of disseminated bronchopneumonia, sometimes multiple miliary abscesses, but no pulmonary gangrene.

During the summer of 1918, one of us had occasion to see a patient whose history would seem to bring new evidence toward the solution of the above problem. The following is a résumé of this observation<sup>6</sup>

CASE 9—Berch, M, a soldier, aged 32 years, presented nothing abnormal from a hereditary standpoint. He had pneumonia at 17, acute dysentery one year ago. The history was one of sudden onset June 9, 1918, with general malaise and pain in the back. June 10 he had a stitch in left side in the region of the precordium, with dyspnea. Cough and expectoration appeared on the following day. On entering the hospital, June 13, he had a temperature of 37.2 C, pulse 100, and moderate dyspnea. His general nutrition might have been better. He was thin, his muscles were poorly developed. There was great prostration. The tongue, covered with a thick, whitish coat, tended to be dry. There was pyorrhea alveolaris. The digestive tract was negative. On examination of the chest, there was found diminution in resonance at the left base, and fine, localized crepitation in the left axilla. Throughout the remainder of the chest, dry râles of bronchitis were heard. The heart was negative. His arterial pressure was 16.9 (Pachon). The urine showed a trace of albumin. In the days following the temperature fell gradually, reaching normal June 22, while the signs of bronchopneumonia increased. The left base became dull, bronchial blowing breathing was heard. Later, June 20, the right base showed similar signs.

Moreover, June 23, fever recurred, the temperature rising to 38.2 C, descending gradually toward normal during the following days. June 29, the patient was afebrile, and remained afebrile until July 9, when there was a moderate new febrile paroxysm lasting several days. By July 12 there was again defervescence, of more than one week's duration without marked change in the condition of the bases posteriorly. The patient did not regain his strength. July 22 the fever again recurred, this time to remain. It was very irregular. The local signs did not vary. Expectoration became abundant, it was mucopurulent and fluid. Tubercle bacilli were sought for on various occasions without results. July 25 the patient expectorated sputum mixed with red blood about twenty times. This symptom caused us once more to incline toward the diagnosis of pulmonary tuberculosis, although examination of the chest revealed no lesions in the apices.

The appearance of a new symptom on August 5 definitely settled the diagnosis. On this day the breath and sputum were found to be very fetid. The nurse had made the same observation during the preceding days without thinking of calling our attention to it. The microscopic examination of the sputum revealed spirilla altogether analogous to those described by Spehl in several cases of fetid bronchitis. Nevertheless, despite the repeated administration of novarsenobenzol intravenously, the situation did not improve. August 16 the expectoration became hemorrhagic. August 17, the patient raised pure blood and died on the eighteenth with abundant hemoptysis.

The necropsy, made by Dr. Colard, showed nothing notable in the heart or digestive tract. The spleen was increased in size and diffuent. No tubercle were found in the spleen, liver or kidneys. The right lung was adherent to the parietal pleura, and the three lobes were glued together by recent adhesions. There was diffuse bronchitis, congestion of the base, no tubercles. The left lung was bound over its whole surface to the parietal pleura by old, thick adhesions. In the upper lobe there was bronchitis without tuberculous lesions. The lower lobe was riddled with numerous cavities filled with foul pus. One of these, situated in the posterior and lower part, was of the size of a large nut. There were, moreover, numerous miliary abscesses. The lung itself was gangrenous almost throughout its lower lobe.

6 Nolf, P. Un cas de gangrene pulmonaire a spirilles, Bull de l'Acad de med. Par 80 657, 1918.

The interesting point about this case lies in the circumstance that it presented at first, the characteristics of secondary spirillar bronchopneumonia, the primary infection being here a grippal bronchopneumonia. There was, however, a clear tendency to pulmonary hemorrhages, and, indeed, it was as a result of an accident of this nature that the patient died. Barring this complication, nothing would have justified a clinical distinction between this case of secondary spirillar bronchopneumonia and the two cases observed above, but the necropsy showed the presence of an extensive gangrene of a lobe of the lung, which was absent, as has been said, in all the cases published by Spehl and me.

It has, therefore, been shown that one may find spirilla similar to those described by us in the expectoration of a patient in which an acute bronchopneumonia becomes complicated at a given moment with pulmonary gangrene. It is probable that this observation will be repeated when in other like cases, spirilla are sought by appropriate methods. It remains to be explained why, in the fatal cases which we have published previously, gangrene was nonexistent.

Two hypotheses may be considered. (1) In rapid diffuse forms, such as in Cases 7 and 8, death may occur before gangrene has had time to develop. (2) In the more circumscribed forms the evolution of which is less rapid, like Case 2, death at a late period seems to have been the result of secondary complications, as is proved by the complete disappearance of spirilla in the expectoration and in the pus of the abscesses—a disappearance brought about probably by arsenical treatment.

If the last hypothesis is sound, the sum of the observations heretofore made would allow us to ascribe to the spirilla a rôle in the production of gangrene.

In the present state of the question, and so far as our observations justify a conclusion, it would seem, then, that spirillar bronchopneumonia is a malady of temperate climes, and that it has probably been confounded up to the present time, with pulmonary gangrene consecutive to acute or chronic affections of the respiratory tract. Its micro-organism is probably a common inhabitant of the upper respiratory passages, particularly of the mouth and pharynx. In this connection it is interesting to observe that the last mentioned patient suffered from pyorrhea alveolaris at the time of his entrance into the hospital.

## BOOK REVIEW

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PULMONARY TUBERCULOSIS By MARIEC FISHBERG, M.D., Clinical Professor of Medicine, New York University and Bellevue Hospital Medical College. Second edition, revised and enlarged. Illustrated with 100 engravings and 25 plates. Philadelphia and New York, Lea & Febiger, 1919.

The author of this work sets forth his object in the preface. The only drawback to this is that prefaces are rarely read, and the reviewer hopes that something may be gained by noting Dr. Fishberg's intentions here. He believes that physicians can and should do more to recognize phthisis in its earliest or pretuberculous stage, that institutional treatment is not the only effective way of handling the phthisical patient, available institutions would hardly accommodate 10 per cent of the eligible patients should all wish to enter, even those who enter sanatoriums require treatment before admission and after discharge, careful home treatment may produce practically the same immediate and ultimate results as institutional treatment and is less costly to the patient and to the community. It would be well if these principles were inculcated into the minds of all classes of the community. It is useless for physicians alone to know them to be true. Since physicians will chiefly use the book, it is worth while to show whether the author has realized his aim in writing it. A critical reading brings the conclusion that the object has been very thoroughly attained. The subject matter is well subdivided and the different chapters have been skillfully treated so that in each one a clear idea is conveyed and at the same time no parts are disproportionately too long or too brief. Realizing that many who read the book have not had recent experience either in laboratories or clinical institutions, the author has adopted a simple, but clear, and on the whole, an accurate way of showing the present state of knowledge of tuberculosis and especially of consumption. The expert may not accept all the views held by the author, but even the expert must admit that the advice given, if acted on, would enormously advance the recognition and care of consumptive patients. Perhaps the pathologic details are discussed too briefly, but the matter will give a good starting point for any physician who wishes to take up the more advanced study and there are useful references to recent original work in all the sections. The social relations are well described. In the chapter on symptomatology, the prevailing errors in practice and the most dangerous pitfalls for the inexperienced investigator are well and fully described. One can see on every page the author's close observation and careful study of clinical medicine as well as of the psychology of the tuberculous individual. The sections on physical diagnosis are particularly full, clear and accurate. Roentgenology is discussed well and clearly, and reproductions of roentgenograms are rather better than the average of their kind. The differential diagnosis is well worked up, and the complications are described well. Under prognosis, the various factors that are concerned are discussed with praiseworthy judg-

ment, while the sections on treatment are full and practical and the measures advised are such as are in favor with the most experienced specialists in and out of institutions. The illustrations, in general, are well chosen and well reproduced. The book has been made up carefully and is well printed. It should find a large audience, particularly among general practitioners.

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Fifty cents each will be paid for the following issues of the Archives of Internal Medicine: January, March, June, August, 1918; January and July, 1916; November, 1915; January, 1911; July, 1909. AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.

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## EXPERIMENTAL PELLAGRA IN WHITE MALE CONVICTS <sup>1</sup>

JOSEPH GOLDBERGER, M D, AND G A WHEELER, M D  
WASHINGTON, D C

Four years ago we published a brief note <sup>1</sup> on a feeding experiment, carried out at the Mississippi State Penitentiary, in which we reported the successful production of pellagra in some white male convicts. Preparation of the detailed report of this experiment was unavoidably delayed by the pressure of continuing field investigations, but has now been completed and is in course of publication <sup>2</sup>. Because of the importance of some new points relating to the etiology of the disease that certain observations in connection with the experiment suggest, it has seemed worth while to present on this occasion a somewhat condensed report of this experiment and of the indications that it affords.

### PURPOSE

The purpose of the experiment was to test the possibility of producing pellagra in previously healthy men by feeding a one-sided, monotonous, principally cereal diet of the type observed by us in other previous studies to be associated with a high incidence of the disease.

### PLAN OF EXPERIMENT

The experiment was carried out at the Rankin farm of the Mississippi penitentiary. The subjects were white male convicts who volunteered for the purpose. White adult males were chosen in order to make the test as rigorous as possible, for, judging by the then available incidence data, this race, sex and age group seemed least susceptible to the disease.

Believing that the significance of the experiment would be enhanced if, in the event of success in producing pellagra, the attack or attacks

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\*From field investigations of Pellagra U S Public Health Service

\*Read in the Section on Pathology and Physiology at the annual meeting of the American Medical Association, New Orleans, April 26-30, 1920

1 Experimental Pellagra in the Human Subject Brought About by a Restricted Diet Public Health Rep 30 3336 (Nov 12) 1915, also Pellagra, Causation and a Method of Prevention, J A M A 66 471 (Feb 12) 1916

2 Bull Hygienic Laboratory, No 121

developed at a season when the incidence and prevalence of the disease were normally on the decline, say in August or September, and having estimated that it would take about three or four months to develop the disease, it was planned to begin with the experimental diet early in May. As the organization of the volunteer squad was completed February 4, this provided a period of three months for preliminary observation. The growing impatience of the volunteers to begin and to get through with their ordeal obliged us, however, to begin the feeding about two weeks earlier than planned, namely, April 19, 1915.

During the preliminary period (February 4-April 19) the volunteers were provided the regular prison fare and were closely scrutinized for any evidence of pellagra that might already have existed. It also afforded time for them to become habituated to the desired routine of work and discipline.

As a condition of volunteering, it was agreed that the men would not be kept on the experimental diet longer than six months. They were freed and, with one exception, passed from observation Nov 1, 1915. The period of the feeding experiment extended, therefore, from April 19 to and including Oct 31, 1915, approximately six and one-half months.

#### CONTROLS AND SUBJECTS

The population of the farm is made up of the prison officials and their families and a fluctuating number of white male convicts.

*Controls*—All persons other than the volunteers resident on the farm during the study were under observation as controls. This included a total of 108 convicts. Of these, thirty were present and under observation from the beginning to the end of the study, of five others, one was present at the beginning and continued under observation to October 26, while four were admitted in February, early during the preliminary observation period, and remained to the end. Practically, therefore, we had under observation a control group of thirty-five convicts for a period comparable to the period of observation of the subjects of the experiment. In age, the members of this control group varied between 19 and 51 years. All denied having had pellagra.

There were resident at the farm a varying number of free individuals (officers and their families) of whom twelve were present throughout the study. Included in this group were six adult males, four adult females and two children, one a boy 12 years of age, and the other a girl 2 years of age. This group is of special interest because of the supposed greater susceptibility of women and children. None of this group of free controls gave a history of pellagra.

*Subjects*—The squad of twelve volunteers, or "pellagra squad," as it came to be called, was organized between February 1 and February 4,

segregated and placed under a special guard employed for that purpose and under our control. The ages of these men varied between 24 and 50 years. None gave a history of having had pellagra, or of the occurrence of the disease in any member of the family or a near relative.

July 1, one of this group was released because of the development of a condition thought to be a prostatitis. This left eleven men who remained in the test to its close.

#### GENERAL ENVIRONMENT

*Farm*—The prison farm is located in Rankin County, about eight miles east of the City of Jackson, Mississippi. It is roughly a square of about 3,200 acres. The country surrounding the farm is sparsely settled.

*Camp*—A little to the north of the center of this farm is located the group of prison, official residence and farm buildings locally designated as the "camp." Near the center of this camp is a fence-enclosed quadrangular area within which are the structures, "cage" etc., in which the general convict population was housed. The volunteers were lodged in the so-called new hospital, a small, one-story cottage, of recent construction, about 500 feet southeast of the "cage" and outside of the stockade. Originally intended for use as the camp hospital, this cottage had served instead as a tailor shop and as quarters for one of the trustees and one of the assistant wardens. By reason of this, the cottage was, by comparison with the quarters of the other convicts, exceptionally clean. In addition it was given a general overhauling and thorough cleaning before the volunteers were lodged therein.

*Screening*—All of the residence buildings and quarters were supposed to be screened. The screening of the general convict quarters was incomplete and defective, that of the cottage occupied by the volunteers was carefully scrutinized and all defects repaired before beginning the study and kept so throughout.

*Water Supply and Sewerage*—This was essentially the same for all sections of the population of the farm.

*Disease Prevalence*—Pellagra is fairly prevalent throughout the county, but, so far as we could learn, no case of this disease had been observed on the farm.

*External Communication*—Although an isolated community, the camp was in frequent communication with the outside world through visitors to the families of the officials and through visiting friends or relatives of the prisoners other than the volunteers. The needs of



the camp made it necessary also for officers or trustees to visit Jackson and other points beyond the farm. While no pellagra is known to have visited the camp during the study, some of the free individuals or trustees may have come into direct contact with pellagra on the occasion of their visits beyond the farm. The volunteers, however, were segregated and under special guard, and no communication was permitted them with the outside except through one of us (G A W) who resided at the camp throughout the study. While, therefore, some of the controls may have come into direct contact with pellagra, such contact was, we believe, absolutely excluded for the volunteers.

TABLE 1—APPROXIMATE COMPOSITION OF THE FOOD CONSUMED BY A GROUP OF CONVICT CONTROLS (THIRTY-FOUR MEN) DURING WEEK ENDING JULY 26, 1915

Food	Quantity Consumed, Pounds	Protein, Pounds	Fat, Pounds	Carbohydrate, Pounds
Biscuit	197.62	17.19	5.14	109.28
Biscuit pudding	57.00	4.96	1.03	20.58
Flour cakes (fritters)	13.25	1.15	0.34	1.31
Corn bread	73.44	3.78	2.35	30.33
Grits	16.25	0.27	0.03	2.45
Rice	23.19	0.41	0.02	5.66
Butter	6.19	0.06	5.26	
Milk, skimmed	264.94	9.00	0.69	13.51
Eggs	2.37	0.31	0.22	
Brown gravy	8.19	0.11	0.03	0.09
Beef gravy	5.31	0.23	0.02	0.06
Beef hash	27.56	5.90	14.25	
Beef liver	1.75	0.36	0.03	0.03
Beef roast	13.12	2.92	3.75	
Salt pork	47.12	3.96	34.26	
Vegetable soup	50.62	1.47	0.10	0.25
Potatoes, Irish	127.12	3.17	0.13	26.57
Cabbage	15.00	0.15	0.05	0.84
Corn on cob	12.75	0.39	0.05	0.98
Cucumbers	6.52	0.07	0.01	0.17
Okra	22.12	0.15	0.24	0.71
Onions, raw	2.86	0.05	0.01	0.28
Peppers, sweet green	4.94	0.36	0.21	1.52
Tomatoes	17.62	0.21	0.07	0.69
Apple pie	17.50	0.54	1.72	7.49
Apples, baked	0.37			0.04
Apples, stewed	21.75	0.07	0.07	2.35
Sugar	34.75			34.75
Syrup, cane	48.75	0.23		36.85
Total		57.47	70.13	296.79
Per man per day (gm.)		110	134	566

*Hygiene*—The quarters of the convict controls were inadequately looked after and were for the most part dirty and vermin-infested. The practice of personal cleanliness was left to the individual, and, therefore, varied within wide limits. In contrast, the quarters of the volunteers were regularly and thoroughly cleaned and free of vermin.

Each volunteer was required to wash hands and face before each meal and to take a full bath at least three times a week

*Work*—The volunteers continued to do a share of the work of the farm. At first the hours of the volunteers were those of the other prisoners, but after beginning the experimental diet the hours were shortened, and when in the field they were allowed a rest period of ten minutes in every hour. The work of the convict controls is rated by us as requiring moderate to hard, that of the volunteers as requiring moderate to light muscular exertion.

*Diet of Controls*—While it varied somewhat from week to week, the character of the diet of the convict controls during the second period of the study is fairly well illustrated in Table 1, for the week ended July 26, 1915. Weighings were made of the food consumed by a group of this class of controls during four sample periods of a week each. Chemical analyses were impracticable, and as in the case of some of the cooked dishes an estimate had to be made of the quantity in place of actual weighings of the individual ingredients, the composition shown in this table (computed by means of the Atwater and Bryant Tables<sup>3</sup>) is an approximation which, while probably fairly close, cannot be regarded as exact. Judged by the indications afforded by the four sample-week periods, summarized in Table 2, the diet of the controls, although tending to be rather high in fat, conformed fairly well to recognized standards. The potential energy varied between 3,500 and 4,000 calories. The intake of protein varied between approximately 90 and 118 gm, that of fat between 95 and 135 gm, and that of carbohydrate between 540 and 580 gm. Approximately, from 20 to 35 gm, or about 20 to 35 per cent of the protein was from animal food.

TABLE 2—SUMMARY OF APPROXIMATE AVERAGE COMPOSITION OF THE FOOD CONSUMED BY SOME OF THE CONVICT CONTROLS PER MAN PER DAY DURING THE SPECIFIED SAMPLE PERIODS

Sample Period, Week Ended	Protein			Fat, Gm	Carbo- hydrate, Gm	Calories	Percen tage of Total Calories Derived from Protein
	Total, Gm	From Animal Food					
		Gm	Percen tage of Total				
June 6	88	29	33	97	568	3,590	10
June 29	97	35	35	117	539	3,695	11
July 26	110	32	29	134	566	4,020	11
Oct 21	92	18	20	96	579	3 645	10

*Experimental Diet*—The volunteers began the experimental diet with the midday meal of April 19, 1915, and continued it up to and including the midday meal of Oct 31, 1915.

The ingredients of the diet were white wheat flour, corn (maize) meal, hominy grits, cornstarch, white rice, granulated cane sugar, cane syrup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens and coffee. In the preparation of biscuits and cornbread "Royal" baking powder was used. Table salt and pepper were freely allowed for seasoning. Up to July 28, buttermilk was used in making the wheat biscuit, this being the same biscuit as that provided the controls. During the week ending June 27, 3 pounds of beefsteak were served at one of the meals, thus giving each man approximately 4 ounces of lean beef on this occasion. No fats other than those occurring naturally in the foods specified were used, the pork fat was extracted from salt pork by frying or boiling. The sirup was home-produced, from "ribbon" sugar cane raised on the farm.

All ingredients appeared to be of excellent quality and, with one or two exceptions, were part of the general camp supply. The principal exception was the maize meal. That of the camp was home-ground from corn raised on the farm and was unbolted. As it was desired to keep the antineuritic vitamin content of the diet low, and as it was believed that the milling might be a factor of importance in this and possibly other respects, we preferred to use a bolted meal, and accordingly provided the volunteers with such. Having in mind the great etiologic significance that had for so long attached to the quality of the maize, we provided the best quality of both meal and grits obtainable on the local market. In order that we might have a biologic check on the quality of these maize products, we arranged to secure our supply from part of that being used at one of the orphanages at which a study of the preventability of pellagra by diet was being made at the time and at which, it may be recalled, no pellagra occurred during 1915. For purposes of additional check, we arranged also that the controls should share with the volunteers the hominy grits thus provided.

The diet served was not absolutely uniform throughout the experimental period, as we felt it necessary by various devices to counteract, from time to time, the tendency of the volunteers to minimize the consumption of maize. There were also individual variations in the diet consumed resulting from individual variations in preference for different foods leading to a certain amount of trading of favorite dishes. Compared with the average diet we have in more recent studies<sup>4</sup> in cotton mill villages found associated with pellagra our experimental diet differed most notably from this in that it was very much more restricted, included no dried legumes, practically no animal

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<sup>4</sup> Goldberger, Wheeler and Sydenstricker. *J. A. M. A.* **71** 944 (Sept 21) 1918, also, *Public Health Rep.* **35** 648 (March 19) 1920.

protein, and included relatively considerable quantities of green vegetables. So far as may be judged by such surface indications, our experimental diet was probably not altogether a typical or average one.

Weighings of food consumed were made for eight periods of one week each. Chemical analyses were impracticable so that the general composition of the diet was computed by means of the well-known Atwater and Bryant tables and the mineral constituents by means of the factors published by Sherman.<sup>5</sup> The results obtained for the week selected as fairly representative are shown in Table 3, and a summary for each of the weighing periods is shown in Tables 4 and 5. Reference to these shows a variation in energy intake of between about 2,500 and 3,500 calories, or a variation of between about 40 and 54 calories per kilo of the average weight of the volunteers. This it will be recognized compares favorably with the requirement by the organism of "35 calories per kilogram of body weight in the average man doing light work on a mixed diet."<sup>6</sup> About 6 per cent of the calories were contributed by the protein.

TABLE 3—APPROXIMATE COMPOSITION OF THE FOOD CONSUMED BY THE VOLUNTEERS DURING THE WEEK ENDING AUGUST 9, 1915  
AVERAGE PER MAN, PER DAY

Article	Quantity, Gm	Protein, Gm	Fat, Gm	Carbohy- drate, Gm	Minerals (in Grams)*							
					Ca	Mg	K	Na	P	Cl-	S	Fe
Cornmeal	176.4	16.23	3.35	133.01	0.032	0.148	0.376	0.069	0.335	0.258	0.106	0.0016
Grits	35.1	3.30	0.25	27.59	0.004	0.020	0.061	0.007	0.071	0.016	0.018	0.0003
Wheat flour	166.9	18.03	1.84	124.84	0.033	0.030	0.192	0.100	0.154	0.124	0.295	0.0017
Rice	30.0	2.40	0.09	23.70	0.003	0.010	0.021	0.008	0.029	0.016	0.035	0.0003
Cane sirup	35.1	0.16	0.00	26.53								
Cane sugar	72.5	0.00	0.00	72.50								
Sweet potatoes	163.1	2.94	1.14	44.69	0.031	0.046	0.645	0.064	0.073	0.153	0.039	0.0008
Cabbage	15.6	0.25	0.05	0.87	0.007	0.002	0.039	0.004	0.005	0.004	0.010	0.0002
Collards	58.9	2.65	0.35	3.71	0.062	0.018	0.302	0.015	0.058	0.010	0.102	0.0011
Pork fat	105.9	0.10	105.65	0.00								
**Total	859.0	46.00	113.00	457.00	0.170	0.270	1.640	0.270	0.710	0.610	0.730	0.0060

\* Not including table salt or baking powder      \*\*Total calories, 3,115

The average intake of protein varied between approximately 41 and 54 gm, that of fat between 91 and 134 gm, and of carbohydrate between 387 and 513 gm. From 80 to 97 per cent of the protein was from cereal sources, practically none was derived from animal food.

Comparison shows the experimental diet and the diet of the controls to be much alike with respect to intake of fat and carbohydrate, and when due allowance is made for the difference in the amount of work done by the contrasting groups, also with respect to energy.

<sup>5</sup> Sherman, H. C. Chemistry of Food and Nutrition, 1918, 2d Ed.

<sup>6</sup> Lusk, Graham. The Elements of the Science of Nutrition, 1917, p. 345.

With respect to protein, however, there are some rather outstanding differences between the two. The intake of this nutrient by the convict controls was approximately twice that of the volunteers, and while from 20 to 35 per cent of the protein in the diet of the former group was from animal sources almost none at all of that in the diet of the latter was derived from this class of foods.

TABLE 4—SUMMARY OF AVERAGE COMPOSITION OF THE DIET OF THE VOLUNTEERS DURING SPECIFIED SAMPLE PERIODS (PER DAY)

Sample Period Week Ended	Protein, Gm	Fat, Gm	Carbo- hydrate, Gm	Total Calories	Calories per Kg	Percentage of Total Calories Derived from Protein
May 27	54	134	513	3,570	54	6
June 21	41	99	426	2,835	45	6
July 12	41	91	387	2,600	40	6
Aug 9	46	113	457	3,115	49	6
Aug 29	46	117	479	3,240	51	6
Sept 13	47	119	481	3,265	52	6
Sept 20	44	114	459	3,125	50	6
Oct 6	44	105	479	3,120	51	6

TABLE 5—SOURCES OF PROTEIN IN DIET OF THE VOLUNTEERS DURING SPECIFIED SAMPLE PERIODS (PER DAY)

Sample Period Week Ended	Total, Gm	From Animal		From Cereal		From Other Foods	
		Gm	Perce- ntage of Total	Gm	Perce- ntage of Total	Gm	Perce- ntage of Total
May 27	54	15	30	440	810	80	16
June 21	41	14	34	330	805	66	16
July 12	41	09	20	370	900	30	8
Aug 9	46	01	03	400	870	58	13
Aug 29	46	01	03	425	920	34	8
Sept 13	47	01	03	438	930	33	7
Sept 20	44	01	03	405	920	30	7
Oct 6	44	01	03	400	910	38	9

With respect to the mineral constituents and vitamins differences can be indicated in very general terms only. The inclusion of milk, butter, peas and beans in the diet of the controls and their complete absence (milk excluded after July 28) from the diet of the volunteers would suggest that the former had a more satisfactory mineral composition and was richer in both the fat soluble and the antineuritic vitamin.

#### RESULTS

Aside from a number of more or less ill-defined ailments and minor injuries, there were observed among our controls a number of rather sharp attacks of malaria, one of appendicitis with appendectomy, one of hemorrhoids with surgical operation, one of probable ureteral cal-

culus, and one of cerebral tumor, but in none was there any evidence justifying even a suspicion of pellagra. It was quite otherwise with the volunteers as may be seen from the following analysis of the manifestations observed among them. The detailed clinical record of each individual cannot, of course, be presented within the limits of the present paper, but will be found in our full report.

#### ANALYSIS OF SYMPTOMS

*First Symptoms*—After instituting the test diet, no complaints to which we would attach any significance were recorded until May 2, when we have a complaint by "A E S" of weakness and dizziness. Six days later another of the volunteers, "A W," brother of the first, made his first complaint, that of epigastric pain. By June 20, all eleven men had begun to complain in one way or another. Eight of the eleven men made their first complaint between May 18 and June 20, that is during the second month of the test diet. Of the symptoms first complained of, weakness, alone or accompanied by some other symptom or symptoms, was mentioned by five. Of the other six men, four mentioned abdominal discomfort or pain (epigastric or right iliac) and two mentioned headache (with nausea in one and "indigestion" in the other) as the first, or among the first, symptoms.

*Weight*—All of the volunteers lost weight, the loss varying between 6 and 22.6 per cent. Comparison of the weight curves of the volunteers with those of a comparable group of controls discloses a very marked difference. The weights of all the volunteers show a general downward trend which is particularly marked during the last four weeks of the experiment. In the control group the weights tend to be stationary or a slight early downward trend is followed by an upward tendency, in none is there any significant loss during the last four weeks.

*Weakness*—In all of the volunteers there developed clear indications of some diminution in strength and vigor. In some this loss was very conspicuous, being shown by an unsteady gait and, when standing, by a tendency to seek for the support of the back of a chair, a table, or a wall. Subjectively, all the men complained of a general weakness. In some there was the additional special complaint of weakness in the legs, and one complained of stiffness in the legs, of which, however, there was no evidence apparent to the observers. At the close of the experiment, all of the volunteers looked worn. In several the objective and subjective indications of weakness and exhaustion were very great, quite out of proportion to the actual loss in weight.

*Headache*—Headache variously localized and of varying degree, both as to intensity and frequency, was complained of by seven of the volunteers

*Pain*—Painful sensations of one kind or another, other than headache, occurred in all eleven men. Pain in the small of the back and abdominal pain or discomfort were of about equal frequency, the former occurring in five and the latter in six of the men. Pain in the side was the next in order of frequency, being recorded in four of the volunteers. In three of these four subjects the pain was in the left side. In all four it was referred to the region of the costal border near the corresponding nipple, or mid-axillary, line.

Pain in the right iliac region<sup>7</sup> occurred in three cases, in the epigastric region (probably dyspeptic) in two, and in the hips in one case. Cramps in the legs and darting pains starting at the ankles and passing upward were complained of by one of the men.

*Nervousness* of varying degree was one of the most nearly constant of the manifestations recorded. It occurred in ten of the volunteers. *Vertigo* occurred in five cases. *Wakefulness* of varying degrees and for varying periods was complained of by five of the volunteers. In some of these, and at times in the others, it appeared to be brought about by some painful sensation (headache, etc.) in others, or at other times, there appeared to be no reason for it other than "nervousness" or restlessness.

*Paresthesias*—Vague nervous manifestations that may be grouped as paresthesias were also noted. Burning in the "stomach" occurred in two cases, and burning in the feet and legs in one. A complaint of a feeling of heat was noted in one of the men. A sensation described as if an acorn had lodged in the chest was spoken of by one, and as if a "knot of something in the stomach" by another.

*Mental Depression*—Apprehension and moroseness of a degree to be decidedly noticeable was recorded in one man.

The *knee jerk* became exaggerated in five of the eleven men. In one it appeared to be reduced and in five no change was recognized. Of the five that were exaggerated the change was noted October 17 in one, and October 24 in four, in all the change was first noted at or shortly after the close of the sixth month of the test diet.

*Digestive Tract*—Reddening of the tongue at tips and margins was noticed in five of the men. In two of these there was also some reddening of the mouth. In all instances the reddening of the tongue was slight to quite moderate in degree. Burning of the mouth was reported

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<sup>7</sup> This pain is very suggestive of appendicitis and we have some reason to believe has occasionally led to operation. The surgeon will do well to keep in mind that pain in the right iliac region may be associated with pellagra.

by one of the men, and in another there was noted a slight increase in the salivary flow. Although complaints of diminished appetite were made at one time or another by nearly all of the volunteers and was fairly marked in at least three of the men, they all, nevertheless, ate fairly well.

Dyspeptic symptoms, including gaseous or acid eructations, were noted in at least five of the men. Vomiting occurred in four and nausea without vomiting was noted in two of the subjects. Gastric analyses were not practicable.

A mild diarrhea, up to three or four watery evacuations a day, occurred in three and a tendency to constipation was noted in one of the men. In seven no change from the normal was noted.

*Skin*—A reddening of the oral commissures with tendency to fissuring was noted in one, and in a second, besides the reddening, there was noted an actual fissuring with a somewhat linear erosion extending for about one centimeter downward and backward on the cutaneous surface.

A well marked dermatitis varying somewhat in extent but bilaterally symmetrical, sharply margined and more or less scaly developed on the ventral or ventrocaudal surface of the scrotum of each of six of the volunteers. The skin of the median raphe retained a normal appearance in all instances. A fairly definite bilateral erythema affecting the scrotum was noted in a seventh and a doubtful erythema on the scrotum of an eighth man. The earliest date of the beginning of this eruption was September 12, or at about the end of the fifth month of the diet. The evolution of these lesions (scrotal) was at first rather slow, so that it was not until very near to the end of the experimental period that they became sufficiently well-defined to permit of more than a suspicion of their significance. In some of the cases this dermatitis was accompanied by slight itching and burning. In one man there were no subjective local sensations, and the lesion on the scrotum might have escaped observation had we not made our examinations after completely stripping each man.

In three of the cases with lesions on the scrotum the erythema or dermatitis extended in some degree to the under surface of the penis, and in two of these there was also some involvement of the prepuce.

In addition to the lesions on the genitalia, three of the men presented lesions on other parts. One presented a slight erythema over the knuckles of the middle and ring fingers of both hands, to which our attention was first called by Professor Haase, one of our dermatologic consultants, one presented a very well marked, indeed, a classical, pigmented, keratosed, bilaterally symmetrical dermatitis of the backs of the hands, and the third a well marked erythema of the dorso-



lateral areas of the deeply tanned skin of the neck<sup>8</sup> The volunteer presenting the lesions at the oral commissures presented no other cutaneous lesions The classically marked dermatitis on the back of the hand, though later in appearing, was of much more rapid evolution than that on the scrotum This and the case with the erythema on the sides of the neck confirmed our interpretation of the nature of the genital (scrotal) lesion in these and the other cases

With respect to *temperature* and *pulse* our data are in such form as to permit only of the general statement that these showed no notable deviation from the normal

*Palpitation* was complained of by two of the men, this should probably be considered a manifestation of indigestion

*Urine*—The conditions under which we worked made it impracticable to regularly secure twenty-four-hour specimens, so that with but few exceptions the urine sample represented that first passed in the morning The results of the examinations of these specimens can, therefore, be interpreted only in a very general way In all instances there was a more or less marked trend to a reduced acidity A tendency to reduced specific gravity was also suggested, but this was not clear We found indican in the urine of at least seven of the volunteers during the period of the test diet In six of these it had also been present before that period, whether this was also the case in the seventh we cannot say, as no examination was made in this instance prior to the beginning of the experimental diet In four of the volunteers indican was detected in the urine before beginning the diet, but none during the course of the experimental period, in two of these indican reappeared in the specimen passed about eighteen hours after return to a high animal protein diet In one albumen present during the preliminary period disappeared after about two months of the test diet

*Diagnosis*—The volunteers were seen with us on three occasions and a diagnosis of pellagra concurred in, in six of the men, by Dr E H Galloway, then secretary of the Mississippi State Board of Health, and by Dr Nolan Stewart, one time superintendent of the Mississippi Asylum for the Insane at Jackson, and among the first to recognize pellagra in Mississippi

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8 In this connection the following from a letter from Professor Haase, referring to one of the volunteers seen by him in Memphis shortly after the latter's release, is of interest "He had not only a sharply margined pigmented lesion on the left side of neck, but two pigmented lesions on right hand over the articulations" Unfortunately, Professor Haase was unable to furnish the name of this man so that he cannot be identified definitely We think it probable, however, that this refers to volunteer "E W H," in which event the lesion on the right hand had escaped our observation or had developed after his release

In excluding the known dermatoses other than pellagra, the special knowledge of Dr Marcus Haase, professor of dermatology in the Medical College of the University of Tennessee, Memphis, Tenn, and that of Dr Martin Engman, professor of dermatology in the Washington University Medical School, St Louis, Mo, were utilized in consultation. In addition to the foregoing, who were formally called into consultation, the subjects were also seen by Drs C R Stingily and F L Watkins of the State Board of Health, and by Dr C H Waring of the U S Public Health Service, all of whom concurred in the diagnosis. In this connection it may be stated that in response to an inquiry (August, 1918) addressed to our dermatologic consultants as to whether they were still of the opinion that the known dermatoses other than pellagra could be excluded in our experimental cases, Professor Engman writes (Sept 4, 1918) "Will say that I am at present even more confirmed in the opinion I gave you three years ago, as to the nature of the eruption on the convicts in the experimental squad, than I was at that time," and Professor Haase, under date of Aug 20, 1918, writes "I have not changed my opinion in regard to cases seen with you and Wheeler at the prison farm near Jackson, Miss. As stated to you then, I knew of no dermatologic condition, except pellagra, that would produce lesions seen, and on my return home looked for early lesions occurring on scrotum and observed two such cases." We may add that in the four years since the close of the experiment we have seen many hundreds of cases of pellagra (over a thousand cases were seen by us in a cotton mill village study in South Carolina in 1917 alone) and this exceptionally large experience with all types of cases has afforded ample additional confirmation of the soundness of our diagnosis in our experimental cases.

It is a not infrequent observation that in a family of several members, although only one may show the distinctive cutaneous lesions, some, if not all, of the others may present subjective and other manifestations which leave little room for doubt that they also are suffering from the same disease. Now, it seems to us, that our squad of volunteers is strictly comparable to a family group, so that it would appear to follow that, having recognized the six cases presenting the skin lesions as pellagra, this diagnosis may properly be extended to apply to the five without the distinctive cutaneous lesions, but presenting the other manifestations. In other words, we are of the opinion that every one of the volunteers developed pellagra, at least six with skin lesions and four or five without ("pellagra *sin* pellagra").

*Discussion* —The fact of the first appearance of the skin lesion on the scrotum in all our cases with definite eruption, suggested to us that the scrotal lesion might be a much more common early skin manifesta-

tion than had theretofore been believed. The literature on this point, at the time of the publication of our preliminary note was, and still is, extremely meager. There existed, so far as we are aware, only two first hand reports of this lesion, a paper by Deiacco<sup>9</sup> and a report by Stannus<sup>10</sup>. In the one case reported by Deiacco the scrotal eruption was not the initial one, but was preceded by lesions in other locations. Although Merk, by implication, clearly suggests<sup>11</sup> that the scrotal lesion may be the first to appear, Stannus seems to have been the first to actually record such cases. In his report of pellagra in Nyasaland, Stannus records nineteen cases (out of 100 with eruption) that presented the scrotal lesion, and of these nineteen, four presented the scrotal lesion alone, whether the scrotal lesion was the first to appear in any other of his cases is not clear from his report. Since the publication of our note a case of pellagra with the initial lesion on the scrotum has been reported by Crosby<sup>12</sup> from South Carolina, and by Wood<sup>13</sup> from North Carolina.

In the course of our study of pellagra in cotton mill villages in South Carolina in 1916, notes were made (by G. A. W.) of twenty-three male cases examined for lesions on the genitals and of finding four with lesions on these parts as the initial site. Of these four cases, one was a first and three were recurrent attacks. Of the twenty-three cases examined, eight were claimed to be first and fifteen recurrent attacks, so that we had one of eight first attack cases with the initial site of the dermatitis on the genitals and three of fifteen recurrent attack cases with this lesion.

This experience would seem to bear out our suggestion that the pellagrous eruption occurs on the male genitalia as an initial lesion much more commonly than the literature might lead one to judge. It remains a fact, however, that the genital lesion, whether early or late, is a somewhat unusual one. Its appearance in all our cases with eruption as the initial lesion is therefore of exceptional interest. It is extremely difficult if not impossible to interpret this as merely a chance phenomenon or as an individual peculiarity. We are inclined to interpret it as a specific reaction, direct or indirect, to some special factor or combination of factors in the diet, and it suggests to us further

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<sup>9</sup> Deiacco, Pius. Ueber lokalisation und natur der pellagrosen hautsymptome, Wien klin Wchnschr **20** 967, 1907.

<sup>10</sup> Stannus, Hugh S. Pellagra in Nyasaland, Tr Soc Trop Med and Hyg **7** 32, 1913.

<sup>11</sup> Merk, Ludwig. Die Hauterscheinungen der Pellagra, Innsbruck, 1909, p. 20.

<sup>12</sup> Crosby, C. E. Pellagra with Erythema of Scrotum as Initial Skin Manifestation, J A M A **68** 1403 (May 12) 1917.

<sup>13</sup> Wood, E. J. The Diagnosis of Pellagra, Arch Diagnosis, **10** 139 (April) 1917.

that the site of at least the initial lesion in pellagra is bound up with a specific quality of the diet. Thus, we are inclined to believe that the dietary fault related to a case of pellagra with the initial lesion on the backs of the hands differs in some essential detail from that associated with a case in which the initial lesion appears on the backs of the feet, etc. It seems to us that we have here, at least, one element in the explanation of some of the reported differences in the manifestations of pellagra in different localities and in the same locality in different years.

#### CONCLUSIONS

Having due regard for the controlled conditions of the experiment, the conclusion would seem to us to be warranted that pellagra developed in at least six of our eleven volunteers as the result of the restricted diet on which they subsisted.

In considering its significance in relation to the etiology of the disease this experiment should be regarded as evidence not apart from but in conjunction with other evidence bearing on this problem. When so considered it is our judgment that this evidence clearly and consistently points to diet as the controlling factor in the causation as well as in the prevention of the disease. We have elsewhere considered at some length the more important evidence in favor of an essential infective etiological factor in this disease<sup>14</sup>. We shall, therefore, confine ourselves here to a consideration of only one of the arguments frequently advanced in its favor. This most commonly takes the following form:

"Inasmuch as bread lines and poor nutrition are of common occurrence in such large cities as New York, Chicago, etc., and as pellagra is of rare occurrence in these places, diet and poor nutrition can have nothing to do with pellagra." More recently this argument has at times been stated as follows: "Inasmuch as the people of Europe, particularly of the Central Powers, have been on starvation diets and necessarily badly nourished, and we hear of no pellagra among them, diet and poor nutrition can have nothing to do with pellagra." Assuming the facts to be as stated, the fallacy in the argument at once becomes apparent when it is pointed out that beriberi, a disease well known to be dependent on a faulty diet, seems to be or to have been no more prevalent than pellagra under the circumstances mentioned. Evidently, then, it does not necessarily follow that, because a disease is the result of a faulty diet, any faulty diet will bring it about. What this argument does suggest, and strongly, is that if poor nutrition favors infec-

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<sup>14</sup> Goldberger and Wheeler. Bull. Hygienic Laboratory, No. 121, also Goldberger, Wheeler and Sydenstricker. Public Health Rep. 35:648 (March 19) 1920.

tion, as is so commonly suggested, then either (1) "poor nutrition" does not predispose to invasion with the hypothetical "infection" of pellagra, or (2) no such "infection" exists, or finally (3) that a specific kind of poor nutrition is necessary to permit the pellagrous "infection" to establish itself

In considering these possibilities, it may be argued that "poor nutrition" does favor invasion with the hypothetical pellagrous "infection" in localities where this "infection" is present in the environment. This would imply that in New York and Chicago, and, incidentally, in our North, as a whole, the pellagrous infection is absent or held in restraint by some unknown factor. As a matter of fact, cases of pellagra, though relatively rare, are by no means of infrequent occurrence in our Northern states and in such cities as New York, Chicago, etc. The hypothetical infection of pellagra is present, therefore, and, it may be added, has been present in this environment at least since the notable epidemic of 1909 at the Peoria (Ill.) State Asylum. Consequently, the important question presents itself. Why is the disease no more prevalent in these cities and in the North generally if poor nutrition favors its invasion? The restraint imposed by the cooler northern climate, the only explanation which suggests itself and one frequently advanced in favor of the relative rarity of the disease in the North, fails as the explanation when it is recalled that in Italy pellagra has for generations been chiefly, if not entirely, prevalent in the cooler northern mountainous section, and that the disease has long been highly endemic in such relatively rigorous climates as those of Bukowina, Transylvania, Roumania and Bessarabia.

In view of these facts, it seems to us that the assumption that "poor nutrition" of a general character favors invasion with the hypothetical "infection" of pellagra, and that this is the explanation of the rôle of diet in pellagra, is untenable. This does not, however, in strict logic exclude the third of the above stated possibilities, namely, that a poor nutrition of a specific kind is essential to enable this "infection" to establish itself. It will at once be recognized that this is identical with the view still held by some with reference to the etiology of such diseases as beriberi and scurvy, namely, that each is due to a specific infection which can arise only in one subsisting on a deficient diet of a specific character.

As in beriberi and scurvy, however, no unequivocal evidence in support of the existence of an essential infective factor in pellagra has yet been adduced. Nevertheless, if in spite of this fact and in spite of the evidence demonstrating the vital rôle of diet in these diseases, one still considers it logical to hold that there is also a second essential extrinsic factor, an infection, in beriberi and likewise one in scurvy, we recognize that it is equally logical to hold a similar view with respect

to pellagra. Clearly, however, even in such event diet is necessarily recognized as the primary controlling element.

#### DIETARY FACTORS

Having evaluated the controlling etiologic influence of diet, we may next seek to determine the factor or factors in the diet which are to be charged with bringing about the pellagra syndrome or syndromes. We have already seen that as relates to quantitative intake of energy, fat, carbohydrate and protein, the experimental diet differed from the diet of the controls significantly only in that the intake of protein was low, though within the limits of recognized standards. These characters of the diet would seem therefore not to be of primary importance, an interpretation which is supported by the results of our studies of the food supply of pellagrous households in cotton mill villages.<sup>15</sup> With respect to the more intimate make-up of the diet, it has previously been noted that the protein was almost exclusively from products of highly milled cereals (wheat, maize, rice). In the light of recent studies, notably those of Osborne and Mendel and of McCollum and associates, this would suggest the probability of a deficiency in intake of some one or more of the amino acids, a probability that would be much increased by the low plane of protein intake. This interpretation is strengthened by the indications afforded by the results of some feeding experiments in rats carried out by Sullivan (Hygienic Laboratory Bulletin No. 121) at the U. S. Pellagra Hospital at Spartanburg, S. C., pointing to the protein as one of the limiting factors of the diet for this species.

The antineuritic vitamin content of the diet was planned to be low and feeding experiments by Sullivan show that the diet was actually deficient in this factor for the common fowl and the pigeon. It is of great interest to note, however, that none of the subjects developed any distinctive clinical manifestations of beriberi, whether they would have done so eventually had they continued on the diet is an interesting speculation.

Judging by the fact that none of the men showed the slightest recognizable indications of scurvy the content of the diet in the anti-scorbutic factor would seem to have been adequate for the period of the experiment at least.

With regard to the adequacy of supply of the fat soluble vitamin, it is difficult to judge by reason of the meagerness of the available fundamental data, none of the men developed any eye symptoms currently considered suggestive of a deficiency in this food essential.

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<sup>15</sup> Goldberger, Wheeler and Sydenstricker. *J. A. M. A.* **71**: 944 (Sept. 21) 1918, also, *Public Health Rep.* **35**: 648 (March 19) 1920.

Compared to the average intake afforded by various American dietaries as compiled by Sherman,<sup>16</sup> the intake of some, at least, of the mineral ingredients in the diet of our volunteers was decidedly low. But whether the mineral intake as a whole or in any of its constituents was actually inadequate or improperly balanced for normal nutrition, it is perhaps impossible to state at the present time, that such may have been the case is rather strongly suggested, however.

It would seem from the foregoing considerations that our test diet was probably faulty in some degree with respect to the protein (amino acid or acids) antineuritic vitamin and mineral constituents. McCollum,<sup>17</sup> as a result of his extensive studies in rats, believes that our diet was also deficient in the fat soluble vitamin. Judging by the results of our field and other observations with reference particularly to the inclusion of dried legumes in the diet of pellagrous households and of individuals, we are satisfied that a deficiency in the antineuritic vitamin is not an essential element in the pellagra producing dietary fault. Similarly the recent observation of the failure to prevent the disease in two individuals who for periods of four to five months before developing the eruption daily consumed the fat soluble vitamin contained in three ounces of creamery butter<sup>18</sup> would seem to indicate that a deficiency in "fat soluble A" is not essential to the production of pellagra. The evidence that we have elsewhere adduced<sup>15</sup> of the preventive value of a meat supplement, coupled with the seemingly small importance that attaches to this food as a source of minerals, would tend to indicate that the mineral factor is of no essential etiological importance. On the other hand, it may be pointed out that the sharp decline in seasonal incidence of the disease, in cotton mill villages of South Carolina, at least, is associated with a great increase in the food supply of green vegetables, a class of foods recognized as important sources of ash constituents in the diet. The facts at hand, therefore, do not warrant a definite judgment on this point. So that of the now generally recognized essential dietary factors, there remain for consideration as possibly essential in relation to the etiology of pellegra, the protein (amino-acids) and the inorganic factor. The determination of which or what combination (or combinations) of these, if any, or whether some deficiency in an as yet unknown dietary factor (vitamin?) alone or in some combination or combinations with one or both of these known factors constitutes the specific pellagra producing dietary defect or defects must await further study.

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<sup>16</sup> *Op cit*, p 271

<sup>17</sup> McCollum and Simmonds. *J Biol Chem* 32 29, 1917

<sup>18</sup> Goldberger and Tanner, unpublished data. The amount of fat soluble vitamin derived from other sources during this period is believed to have been negligible.

## SUMMARY

1 An experiment was carried out at the Rankin farm of the Mississippi penitentiary to test the possibility of producing pellagra in previously healthy men by feeding a monotonous, principally cereal, diet

2 The subjects of the experiment were eleven white adult male convicts who volunteered for the purpose. They were segregated and kept under special guard. None gave a history of having had pellagra or of the occurrence of this disease in any member of the family or a near relative.

3 All persons other than the volunteers resident on the farm were under observation as controls. This included 108 convicts, of whom thirty-five were under observation for a period comparable to the period of observation of the subjects of the experiment. In addition there were twelve free persons who were present throughout the study, included in these were four adult females and two children.

4 The general sanitary environment was the same for subjects and controls. With respect to personal cleanliness, cleanliness of quarters, and freedom from insects and vermin, the volunteers were decidedly better off than the convict controls.

5 No direct communication with the outside was permitted the volunteers. There was no special restriction imposed on the controls, convicts or free. Direct exposure of some of the controls to a hypothetical infection was possible and may have occurred when beyond the limits of the farm, this possibility is believed to have been excluded in the case of the subjects of the experiment.

6 The volunteers continued to do a share of the work of the farm, but, when compared with the convict controls, they had shorter hours of work and had regular rest periods when in the field. The work of the convict controls is rated as requiring moderate to hard, that of the volunteers as moderate to light muscular exertion.

7 The study falls into two periods, one extended from February 4 to April 19, during which the volunteers were kept under observation without any change in the regular prison fare, the second period extended from April 19 to and including October 31, during which the volunteers subsisted on the experimental diet.

8 The average intake by the convict controls, as shown by four periods of a week, each varied between approximately from 3,500 and 4,500 calories, between 90 and 110 gm of protein, 95 and 135 gm of fat, and between approximately 540 and 580 gm of carbohydrate. Approximately from 20 to 35 per cent of the protein was from animal food.



9 The ingredients of the experimental diet were highly milled wheat flour, maize meal and grits, cornstarch, white rice, cane sugar, cane sirup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens, coffee, "Royal" baking powder, salt and pepper. During the first three months some buttermilk was used in making wheat biscuits. All ingredients were believed to be of excellent quality and, with one or two exceptions, were part of the general camp supply. In its essential make-up the experimental diet was probably not entirely typical of the average pellagra producing diet.

10 The average intake by the volunteers, as shown by eight periods of a week each during the experimental period, varied between 2,500 and 3,500 calories, between 41 and 54 gm of protein, between 91 and 134 gm of fat, and between 387 and 513 gm of carbohydrate.

11 Although both classes of controls (convict and free) were exposed to the chance of direct contact with pellagra and although, as compared with the volunteers, the convict controls were at a disadvantage hygienically, and were required to work harder and furthermore, although various minor ailments and a number of rather sharp attacks of malaria were observed among them, none of the convict (or other) controls developed any evidence of pellagra. On the other hand, although segregated and under special guard and the possibility of direct contact with pellagra excluded, and although under much more favorable hygienic conditions, not less than six of the eleven volunteers who remained in the test to the end developed evidence which experienced observers joined with us in recognizing as those of pellagra.

12 Significant subjective symptoms made their first appearance among the volunteers during the second month after beginning the test diet. These included weakness, abdominal discomfort or pain and headache. All subjects lost weight, the loss becoming particularly marked during the last four weeks of the experiment. At least six of the eleven men developed a well-marked eruption. The earliest date of the beginning of this was September 12, or at about the end of the fifth month of the diet. The initial site in all of the cases was the scrotum, later classical lesions also developed in one on the hands and in another on the neck. The knee jerk became exaggerated in five of the men, the earliest date being October 17, at the close of the sixth month of the experiment.

13 Having due regard for the controlled conditions of the experiment the conclusion seems warranted that pellagra developed in at least six of our eleven volunteers as the result of the diet on which they subsisted.

14 The scrotal lesion is a much more common early skin manifestation of pellagra than has heretofore been realized, but is nevertheless a somewhat unusual one.

15 It is suggested that the site of at least the initial dermatitis accompanying an attack is bound up with a specific quality of the diet. The view is advanced that there exist essential differences in the intimate make-up of the diet corresponding to observed differences in some, at least, of the clinical types of the disease.

16 In relation to the production of pellagra, the dietary factors to be considered as possibly essential are (1) an amino-acid deficiency, (2) faulty mineral supply or constitution and perhaps (3) an as yet unknown (vitamin?) factor. As to which or what combination, or combinations, of these constitutes the specific pellagra-producing dietary defect or defects remains to be determined.

The experiment herein described was made possible by the hearty cooperation of Governor Earl Brewer and Dr. E. H. Galloway, of the State Board of Health of Mississippi, to both of whom our grateful acknowledgments are due. We are indebted to Dr. Galloway also for his interest and aid as one of our consultants. Our thanks are due also to Dr. Nolan Stewart and Professors Haase and Engman for their valuable assistance as consultants. To Dr. A. G. McLaurin of Brandon, Miss., prison physician since 1909, we are indebted for information relative to disease prevalence at the prison farm and to Drs. Stingily, Watkins and Waring we are indebted for their interest and for many helpful courtesies.

# EXPERIMENTAL PULMONARY EDEMA <sup>\*</sup>

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The following summary of the literature on pulmonary edema is to serve as a background for the present great interest in pulmonary edema stimulated by the work done on gas poisoning in the battle areas and in the laboratories. It was decided that the purpose of our work could be best fulfilled if an accurate recital of the experiments and data on experimental lung edema were chronologically arranged. The interjection of personal opinion and interpretation, therefore, is reserved until after the recital of the data.

In a study of the papers which might give information concerning the cause of pulmonary edema, it was found that the results could be grouped in the following order: (1) Lung edema occurring as an incident in an experiment, (2) lung edema produced for study, (3) lung edema recognized as a feature in an experiment, but its immediate cause overlooked or neglected. For this review, the second group is, of course, the most instructive and most deserving of attention, while the other two groups are suggestive.

## HISTORICAL REVIEW

Virchow,<sup>1</sup> in 1853, produced pulmonary edema by injecting fat into a jugular vein. The mechanism was not investigated.

Pokrowsky,<sup>2</sup> while studying carbon monoxid poisoning in cats, dogs, rabbits and frogs, occasionally obtained lung edema. He was confirmed by Friedlander and Herter.<sup>3</sup>

Falk<sup>4</sup> studied the effect of gases and poisons on the glottis primarily. He was interested in the occurrence of spasm, and observed lung edema in mammals during chlorine gas poisoning.

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<sup>†</sup> The data in this paper were prepared originally for the Chemical Warfare Service as confidential matter in furthering the study of toxic war gases. Permission to publish has been granted.

1 Virchow. Virchows Arch. 5 308, 1853.

2 Pokrowsky. Carbon Monoxid Poisoning, Virchows Arch. 30 525, 1864.

3 Pokrowsky, Friedlander and Herter. Carbon Dioxid Rich Atmosphere to Rabbits Get Various Grades of Pulmonary Edema, Cohnheim's Allg. Path., Ed 2, 1 502, 2 273, 1882.

4 Falk. Spasmus glottidis bei gewaltsamen Todesarten, Viertelj. gericht. med. 16 6, 1872.

Friedländer<sup>5</sup> ligated the ascending aorta proximal to the innominate artery in the rabbit. The animal died in a short time and postmortem examination showed lung edema.

Longet<sup>6</sup> (from Chemery) noted the occurrence of lung edema after vagal section. (See also von Frey<sup>7</sup>)

Schweninger<sup>8</sup> noted that fat emboli led to acute lung edema. This was confirmatory of Virchow's work.

Lassar<sup>9</sup> studied the effects of acid vapors: nitric, sulphuric and hydrochloric, and of iodine on dogs and rabbits. The vapors rarely induced a bronchitis or a bronchopneumonia when sufficient air was mixed with them. In a few instances, lung edema occurred after asphyxia. He noted the nonappearance of acids in the urine, and stated that either the acids do not diffuse through the alveolar walls or they are precipitated higher up in the respiratory passages, in which case they may unite with the lung epithelium before they can get through. Their danger lies in the fact that they lower the oxygen percentage of the inspired air, producing asphyxial symptoms.

Cohnheim and Lichtheim<sup>10</sup> morphinized or curarized dogs and rabbits, and then injected enormous quantities (from 64 to 92 per cent of the body weight) of a 0.6 per cent solution of sodium chloride at body temperature intravenously. In several cases exitus occurred in a few hours with symptoms of acute pulmonary edema. The dogs had a decreased dry weight of the blood. Arterial pressure was increased temporarily or not at all, while the venous pressure rose slightly or not at all, but never came back to zero if it did rise. The pulse frequency was not increased. There was an increased velocity in the blood stream, and an increased lymphatic flow. There was a marked outpouring of fluid in the glandular organs although none in the skin, central nervous system, or thoracic cavity. The blood count was uniform in the portal, jugular and femoral vessels. They say that venous stasis is not responsible for the edema. They also injected distilled water, a 3 per cent glucose solution, various salt solutions and diluted blood serum, and obtained similar results. Merely replacing the blood was negative. Their view is that the capillaries vary in permeability and they felt that this was proven by obtaining skin edema in these animals after wounding the skin or painting it with iodine or exposing the shaved abdomen to the sun's rays.

5 Friedländer. Untersuchungen über die Lungenentzündung. Berlin 1873.

6 Longet. Physiologie, Ed 3 2 507 1873 (see Chemery).

7 Von Frey. Die Pathologischen Lungen-Veränderungen nach Lähmung der nervi vagi. Leipzig, 1877.

8 Schweninger. Aertzliches Intellig. Blatt 1876.

9 Lassar, O. Ueber irrespirable Gase. Ztschr. f. Physik. Chem. 1.165 1877.

10 Cohnheim and Lichtheim. Ueber Hydrämie. Virchows Arch. 69.106 1877.

Welch,<sup>11</sup> in the *first extensive research on pulmonary edema per se*, raised issues which challenged the attention of many workers. He reviews the causes of pulmonary edema postulated by others, such as increased heart activity, direct irritants, collateral hyperemia, thinning of the alveolar air, effect of cold drinks, inflammatory conditions, stasis—pulmonary vein obstruction or weakened heart action with both chambers equally weak. He says that the mechanical factors have not been exhausted, and that a stasis edema is possible by the production of obstructions in the lung veins, left auricle, left ventricle and aorta. He produced lung edema in dogs and rabbits, more easily in the latter. Tying the aortic arch between the innominate and left subclavian arteries produced lung edema in only one rabbit, while tying two additional branches of the innominate artery resulted every time in lung edema accompanied by asphyxial phenomena. It requires almost complete occlusion of the aorta between the heart and the innominate artery to get an edema. Lung edema occurred when the pulmonary artery pressure rose. The carotid pressure usually rose. The stasis occurs because more blood goes to the heart than comes away, and the stasis is not due to weakness of the right ventricle. These methods, however, he says, are not applicable to human cases, nor are they comparable to what occurs in the human being. Ligation of pulmonary veins must be extensive before edema occurs, while pulmonary artery pressure rises slightly until the onset. Welch emphasized the fact that marked pressure on the left auricle and left ventricle produced lung edema in the rabbit. The microscopic picture resembles that found in man. Welch postulated a disproportion between the working power of the ventricles with the left less efficient than the right. He attempted to produce a onesided cardiac paralysis by the use of potassium, iodine, salts, carbon monoxide and strychnine internally, while potassium salts, chloroform, ice and heat were applied externally. At last, he succeeded in producing such a paralysis by squeezing the left ventricle of rabbits with his fingers. He never obtained edema by pressure on the right ventricle alone, or by pressure on the right and left ventricles. He believes that the increased capillary pressure in the lung vessels is added on to the greater permeability of the lung capillaries. Too much emphasis should not be laid on the fact that the pulse is weak in some human cases. Microscopic section showed distended capillaries filled with red blood corpuscles. Red blood cells were also found in the interstitial tissue.

Rosenbach,<sup>12</sup> while studying artificially produced valvular insufficiency, obtained pulmonary edema in two cases. His postmortem

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11 Welch. Zur Pathologie des Lungenödems, Virchows Arch 72 375, 1878

12 Rosenbach, O. Ueber Artificielle Herzklappenfehler, Arch f Exp Path u Pharm 9 1, 1878

examination findings inclined him to accept Welch's view of unequal activity of the ventricles

Lichthelm<sup>13</sup> produced pulmonary edema in rabbits by ligation of the artery and veins at the hilus. This occurred when the ligation was done unequally, by which he meant that the inflow had not ceased while the venous outflow had. These lungs had the same appearance as in those experiments in which only the pulmonary veins were tied.

Mayer<sup>14</sup> confirmed Welch's findings. Ligation of the innominate and left subclavian arteries in noncurarized animals leads in most cases to marked edema with strong convulsions. In curarized animals no such results follow. He quotes Kussmaul and Teuner who produced pulmonary edema by ligating the arteries going to the head as indicating the importance of asphyxia as a cause of edema. Mayer obtained some results by ligating four main aortic branches. He believes that the variation in intensity of edema is due to (1) increased vascular tension, (2) vessel tonus, and (3) the milking effect of the right ventricle, and that these factors are especially present when asphyxial convulsions occur. Opening the abdomen and combining vessel ligation with the production of a double pneumothorax, so as to eliminate the mechanical effects of convulsions, prevented the occurrence of edema.

Sahl<sup>15</sup> endeavored to repeat Welch's results, but failed in most cases. In some cases, ligation of the aorta and pressure on the left auricle produced a rise in pulmonary artery pressure, followed by a lung edema in dogs and rabbits. He says, however, that such methods are crude and not applicable to human conditions. He minimizes convulsive factors on the basis of strychnin experiments in which he got high lung artery pressures. Even when the pulmonary artery pressure is high and the carotid pressure is low, no edema need result. Cohnheim, in 1876, showed that marked changes in the systemic circulation have little effect on the pulmonary circulation. A paralysis of the left ventricle need not produce lung edema in dogs. Pressure, clamping, isolated faradization, narrowing of coronary vessels and injection of cardiac poisons were all negative. In man, he reiterates, lung edema is possible where *both* ventricles are *weak*, as in a case of combined aortic and mitral insufficiency. Then, again, a majority of the lung edemas in man are of inflammatory origin in the lung itself. His experiments with hydrocyanic acid were negative.

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13 Lichthelm. Versuche über Lungenatelektase, Arch f Exp Path u Pharm **10** 71, 1879

14 Mayer, Sigmund. Experimentale Pathologie des Lungenödems, Sitzberichte d k Akad d Wissensch Wien **77** Part 3

15 Sahl. Zur Pathologie und Therapie des Lungenödems, Arch f Exp Path u Pharm **19** 433, 1885

Martin,<sup>16</sup> perfusing the mammalian heart with defibrinated blood, notes the frequent, unfortunate interruption of the experiments by the onset of lung edema. He was primarily interested in the activity of the heart itself.

Tigerstedt and Santesson<sup>17</sup> filled freshly removed frog's lungs with 0.6 per cent sodium chlorid solution and found that they withstood a pressure of 14 mm Hg for several hours, whereas, if the lungs were injured by heat, or by pouring into them distilled water or frog's bile, filtration is obtained at once.

Lehmann<sup>18</sup> obtained lung edema by exposing cats, rabbits and guinea-pigs to hydrochloric acid and ammonia vapors. He includes a microscopic description of the lungs. Lehmann probably deserves credit for his prophetic insistence that poisonous (irrespirable) gases deserve and require intensive experimental study with the development of proper technic. He quotes and criticizes Eulenberg,<sup>19</sup> Lewin<sup>20</sup> and Hirt.<sup>21</sup> The work of Hirt is discredited by him, even though Hirt was widely quoted as an authority at the time. Eulenberg studied a number of irritating gases somewhat superficially, he says, and without proper attention to oxygen supply and carbon dioxide removal. Lewin is at fault because he uses Hirt's data. Lehmann experimented with a gas mask in a gas-filled room. His experimental method provided oxygen supply and carbon dioxide removal by means of a modified Pettenkofer-Voit respiration chamber. It may here be stated, that many of his reports on gas effects state the mere fact that a lung edema occurred, but there is little attempt to study the sequence of symptoms, their interrelation, significance and cause singly.

Pettenkofer<sup>22</sup> reported the studies on irrespirable gases of his pupils (Gruber, Ogata, Lehmann, Nakahama and Mori) to the Munich Academy of Scientists. He emphasized Lehmann's results on guinea-pigs, cats, rabbits and man. Lung edema appeared with toxic doses of hydrochloric acid, ammonia, chlorine, bromine, hydrogen sulphide, carbon disulphide and aniline. Nitrobenzol was negative. The toxicity of all

16 Martin. A New Method of Studying the Mammalian Heart, Studies from Biological Laboratory, Johns Hopkins University 2 118, 1882.

17 Tigerstedt and Santesson. Bignang till K. Svensk Vet. Akad. 11 No. 2, 1886.

18 Lehmann, K. B. Experimentelle Studien über den Einfluss technischer und hygienischer wichtiger Gase und Dämpfe auf den Organismus (Ammoniak und Salzsäuregas), Arch. f. Hygiene 5 1, 1886.

19 Eulenberg. Die Lehre von den schädlichen und giftigen Gasen, Braunschweig, 1865, Gewerbe Hygiene, Berlin, 1876. See Reference 18.

20 Lewin. Lehrbuch der Toxicologie. See Reference 18.

21 Hirt. Die Gasinhalationskrankheiten, Breslau, 1873. See Reference 18.

22 Pettenkofer. Ueber Gesundheitschädlichkeit mehrerer hygienischer und technischer wichtiger Gase und Dämpfe, Sitz.berichte d. k. bayer. Akad. d. Wissensch. zu München 17 179, 1887.

the substances was determined. Hydrochloric acid was toxic to mammals in 1/10,000, a figure markedly different from those previously reported. Chlorin poisoning was followed by a narcotic effect.

Grossmann<sup>23</sup> noted the appearance of lung edema following muscarin injection. Curarized dogs were used. Lung capacity, venous, carotid, pulmonary artery and left auricle pressures were recorded. He gives credit to von Basch for observing this type of edema first. After muscarin injection he claimed that there was a rise in venous pressure, right auricle pressure and left auricle pressure, and a fall in aortic pressure. Atropin administration and accelerator stimulation was followed by a disappearance of the muscarin induced lung edema. The blood flows slowly through the lung capillaries and under a high pressure. Section of the splanchnics or cervical cord did not prevent lung edema occasioned by muscarin. Strychnin was ineffective. Decreasing the amount of blood from the right ventricle prevented the appearance of the edema. Intravenous (jugular) injection of physiologic sodium chlorid solution caused signs of edema to disappear. Muscarin produced a decrease in the size of the left ventricle, and an increase in size of the right ventricle. Vagal stimulation dilated both ventricles. Muscarin probably produces a spasm of the left ventricle. Grossmann obtained stasis edema in eighty-five dogs with intact cardiac valves and strong pulses.

Grossmann, von Zeissl (*vide infra*) and Winkler (*vide infra*) are pupils of von Basch who claimed that (a) increased lung volume and (b) diminished expansibility of the lungs followed after increased filling of the lung vessels. They used special apparatus to record lung volume changes. The von Basch theory, if not discredited, at least is not accepted at present.<sup>24</sup> His pupils go a step further in postulating the occurrence of lung edema if (a) and (b) persisted as shown in their tracing without verification very often of the presence of an edema by direct examination of the tissues.

Sahli,<sup>25</sup> in a polemic against Grossmann, reiterates his criticism of Welch as the proponent of the left ventricle weakness theory of lung edema which Grossmann supports, in the main. He states also that spasm of the left ventricle and low blood pressure should be accompanied by signs of arterial anemia. Of course, clinically they are not. Therefore, Grossmann's low blood pressure data and other factors are at variance with clinical facts. The von Basch theory is completely thrown out of court. Sahli says that he obtained high pulmonary

23 Grossmann. A Study of Acute General Lung Edema. Muscarin lung edema, *Ztschr f klin Med* **12** 559 1887.

24 Heinz. Handb d Experimentellen Pathologie und Pharmakologie **2** 514, 1906.

25 Sahli. Pathologic Lung Edema, *Ztschr f klin Med* **13** 482, 1888.



artery pressures for hours and still got no edema, therefore he doubts whether Grossmann could get any edema during a short period of high pressure

Grossmann<sup>26</sup> describes the microscopic and gross changes in the lungs of cases of muscarin edema. The carotid pressure served as an index of what was occurring in the pulmonary artery. He dilates further on the von Basch theory that a more than normal filling of the blood vessels is followed by an increase in the alveolar space. He does not believe that muscarin narrows the bronchioles. The intrapulmonic air space decreases before there is cardiac slowing, then it increases. With carotid bleeding, the diminished expansibility of the lungs is reduced. In one series he put physiologic sodium chlorid solution into the trachea, as much as 600 c c in one experiment, without changing the lung capacity. He answers Sahli by saying that lung edema can be produced in dogs by compression of the left ventricles.

Grossmann<sup>27</sup> later returned to the von Basch theory with a study of obturation of the right auricle and left ventricle.

Lowit<sup>28</sup> criticizes Grossmann for postulating pulmonary artery pressure from carotid pressure when neither Knoll nor Lowit find constant effects in the pulmonary artery pressure by asphyxiation or aortic compression. Cats and rabbits were used after receiving hirudin. Marked compression of the aorta can produce simultaneous pressure rises in the pulmonary artery or in the left ventricle, or in one alone, or no rise at all. Therefore, the condition of the pulmonary artery pressure cannot be postulated from an examination of the left auricle pressure. He criticizes Grossmann's method of diagnosing lung edema. The best test is the transudate. Compression of the aortic root also produces varying results. Narrowing the tricuspid lumen to one third of the original opening hinders the outflow of blood to the right heart, resulting in a fall in pulmonary artery pressure. A large amount of blood can be accommodated by the pulmonary circuit without producing edema. Salt injection in the jugular, plus aortic root clamping, always resulted in lung edema. With an obstructed outflow of pulmonary blood, and an increased inflow of pulmonary blood lasting for some time, a stasis edema results in curarized or noncurarized animal, although sooner in the latter. He agrees with Mayer as to the importance of accessory factors. Marked compression of the left ventricle resulted in edema only when the pulmonary artery pressure rose,

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<sup>26</sup> Grossmann. Acute General Edema, *Ztschr f klin Med* **16** 161, 183, 270, 310, 1889

<sup>27</sup> Grossmann. Lungenschwellung u Lungenstarrheit, *Ztschr f klin Med* **20** 397, 1892

<sup>28</sup> Lowit. Ueber die Entstehung des Lungenodems, *Beitr z Path anat u z allg Path* **14** 401, 1893

therefore, he disclaims left ventricle weakening as the cause. He maintains that Welch obtained his edema following asphyxia. He has often noted no volume increase in lungs with edema, and often marked volume increase in lungs after muscarin with no lung edema. Double vagotomy results in inflammatory edema after from one to two hours, because Knoll showed that vagotomy produces no change in the small circulation. The pressure changes are negative.

Toxic lung edema was next considered by him. His studies with muscarin led to different results than Grossmann's. The pulmonary artery pressure rises, while the left auricle pressure rise is only temporary and coincident with the cardiac slowing. Lowit never got a lung edema with muscarin. Intravenous injection of acetic ether produced lung edema and transudation in other parts of the body. Lowit postulates vascular wall changes. Sulphuric and butyric ether act similarly. These types resemble the following in man: (1) Acute general edema, (2) inflammatory, (3) agonal, and (4) direct irritants of the lungs. Lung edema can be produced experimentally by excessive artificial ventilation. This is not accompanied by any pressure changes as a rule, therefore, it is not of stasis origin. Von Kahldeen (1895) abstracted his article.

Alexandrow,<sup>29</sup> in the main, confirms Welch, but in addition introduces nerve section and infusion experiments. Vagotomy is followed by edema. Lung capacity is lessened when there is blood stasis in the lung vessels. Artificial respiration delays the onset of lung edema. Section of recurrent nerves and accessories, or section plus hindrance to ingoing air is followed by lung edema. He worked with dogs, cats and rabbits.

Von Zeissl<sup>30</sup> produced lung edema in dogs by intravenous injections of iodine solution. He follows von Basch in his interpretations, and gets practically the same changes as Grossmann does with muscarin. In one experiment the lung edema was accompanied by a fall in the left auricle pressure. Morphinized and nonmorphinized animals were used with thorax both intact and open.

Jacoby<sup>31</sup> discusses the technic of perfusing surviving lungs while under artificial respiration. The onset of edema is earlier the more dilute the blood is made. In these isolated lungs, with edema present, he hypothesizes a disturbance of the gas exchange mechanism.

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29 Alexandrow. Ueber Die Entstehungsweise des Stauungsödems in den Lungen, Diss. Moskau, 1892, Abstr. *Centralbl. f. allg. Path. u. path. Anat.* 4, 691, 1893.

30 Zeissl. Ueber Toxisches Lungenödem, *Centralbl. f. Physiol.* 7, 702, 1893, *Ztschr. f. klin. Med.* 27, 363, 1895.

31 Jacoby, C. Ein Beitrag zur Technik der Künstlichen Durchblutung überlebender Organe, *Arch. f. Exp. Path. u. Pharm.* 36, 530, 1895.

Grossmann<sup>32</sup> returns to the further elucidation of the von Basch idea. He claims that pulmonary artery pressure and left auricle pressure need not be registered simultaneously. Obturation of the left auricle produces a fall in carotid and venous pressures, accompanied by a marked rise in pulmonary artery pressure. The fall in venous pressure is interpreted as being due to the diminished amount of blood coming to the right heart. In this set of experiments Grossmann postulates that swelling of the lungs and their diminished expansibility is an invariable accompaniment of increased lung artery pressure, on the basis of his previous experiments. Compression of the root of the aorta causes a fall in carotid, and a rise in pulmonary artery and left auricle pressures. Fluid injected into a pulmonary vein produces the same result. In a polemic against Lowit, he believes that Lowit had clots in the blood vessels in spite of using leech extract, and that Lowit included the pulmonary artery often on aortic compression. He states, again, that the left auricular pressure rise is not directly related to the muscarin heart slowing. This rise is caused by the left ventricle spasm, and is followed by stasis hyperemia, which, in turn, are succeeded by lung swelling and diminished expansibility.

Lowit<sup>33</sup> answered Grossmann's critique.

Benedicenti<sup>34</sup> reported the occurrence of lung edema in mammals following inhalation of 25 to 30 per cent carbon dioxide.

Winkler,<sup>35</sup> in administering amyl nitrite to curarized and morphinized animals, obtained lung edema with the typical carotid fall by nitrites. He is a pupil of von Basch, and used Grossmann's methods. Tigerstedt<sup>36</sup> cited the work of Bradford and Dean that a carotid pressure fall is accompanied by a pulmonary artery pressure rise. Tigerstedt states that amyl nitrite weakens the left heart.

Kockel<sup>37</sup> incorporates Weltzel's data with his own on the effect of nitric and nitrous acids on man and animal (rabbits, mice, guinea-pigs). He cites Bauer<sup>38</sup> as having the same results. After gassing, there is a period of relatively good health before untoward symptoms

32 Grossmann. Stauungshyperämie in den Lungen, *Ztschr f klin Med* 27 151, 1895.

33 Lowit. Polemic vs Grossmann, *Centralbl f allg Path u path Anat* 6 97, 1895.

34 Benedicenti. Die Wirkung der Kohlensäure auf die Atmung, *Dubois Arch*, 1896.

35 Winkler. Neue beiträge zur Kenntniss des Amylnitrits, *Ztschr f klin Med* 35 213, 1898.

36 Tigerstedt. *Ergebn d Physiol* 2 581, 1903.

37 Kockel. Ueber das Verhalten des menschlichen und thierischen Organismus gegen die Dämpfe der Salpetrigen und Untersalpetersäure, *Viertelj f gericht Med* 15 1, 1898.

38 Bauer. Festschrift zur Feier der 50 Conf des Vereins d Medicinalbeamten d Kg-Bez, Dusseldorf, 1895.

occur Lung edema and inflammation of the respiratory passages are the most prominent symptoms Microscopic sections show multiple hyalin thrombi in lung vessels The injured regions become foci for bacterial invasion The respiratory epithelium is desquamated The heart is weakened and this adds to the initial lung edema The decreased gas exchange yields a third factor conducive to the production of edema Death is by asphyxiation There is a direct local effect on the lungs

Kunkel<sup>39</sup> presents a general discussion of "gaseous" poisons, symptoms and pathology, and refers in general terms to his own experiments He outlines the following problem as to the distribution of the gas or vapor (1) the part bound to the tissue, (2) the portion absorbed, changed or unchanged, (3) the portion resorbed, and (4) the amount excreted again via the lungs

Magnus<sup>40</sup> reviews Cohnheim and Lichtheim's work, confirms it, and cites Fleischer, Dembrowski, Dastre and Loye, and Knoll as having confirmed it He also reports on his experiments with arsenic in producing pulmonary edema

Founeau's thesis<sup>41</sup> contains no original experimental work

Carrion and Hallion<sup>42</sup> injected salt solutions of various concentrations intravenously, and noted the occurrence of acute pulmonary edema They give no tracings or records of their experiments

Chatin and Guinard<sup>43</sup> record the occurrence of lung edema after the injection of methyl salicylate

Miecamp<sup>44</sup> follows Teissier, his teacher, with emphasis on theory. He presents no original work

Chanoz and Doyon<sup>45</sup> showed lung edema after injecting amylsalicylic ether intraperitoneally or intravenously Death resulted from arrest of respiration There were convulsions

Winterstein<sup>46</sup> records lung edema and increased mucosal secretions in animals after carbon dioxide inhalation

D'Achard and Loeper<sup>47</sup> confirm Carrion and Hallion

39 Kunkel *Handb d Toxikologie* 1 38, 1899

40 Magnus *Die Entstehung der Hautödeme bei experimenteller hydrämischer Plethora*, *Arch f exper Path u Pharmakol* 40 252, 1899

41 Founeau *De l'œdème aigu du poulmon*, These, Paris, 1898

42 Carrion and Hallion *Contributions experimentale a la pathologie des œdèmes*, *Compt rend de la Soc de Biol* 51 156, 1899

43 Chatin and Guinard *Recherches pharmacodynamiques sur le salicylate de methyle*, *Ibid*, 52:669, 1900

44 Miecamp *Pathogenie de l'œdème aigue du poulmon*, These, Lyon, 1900

45 Chanoz and Doyon *Compt rend Soc de Biol* 52 716, 1900

46 Winterstein *Engelmann's Arch*, Suppl, 1900

47 D'Achard and Loeper *Sur la retention des chlorures dans les tissus au cours de certains etats morbides*, *Compt rend Soc de Biol* 53:346, 1901

Teissier and Guinard<sup>48</sup> used methyl salicylate to produce edema. After curarization, artificial respiration was instituted following tracheotomy. A window in the left thorax permitted them to get the pulmonary artery pressure. Compression of the aorta was negative, except for a temporary rise in pulmonary pressure and a fall in carotid pressure. Injection of methyl salicylate produced no effect or only a slight rise in the pulmonary artery pressure. Stimulation of vagi, plus the drug, produced lung edema, but edema was not marked when the heart was irregular. They also recorded left auricular pressure. There is no need, they say, to produce a rise in the latter pressure in order to get lung edema. The left auricle pressure does not change at all after the drug is injected, while the carotid pressure gradually falls. They propose a mixed theory. First, mechanical difficulties are of themselves insufficient, second, nervous effects, such as vasodilation, plus the first, facilitate an occurrence of lung edema, but third, an intoxication is necessary to produce an edema.

Bouchard and Claude<sup>49</sup> confirm Josue<sup>50</sup> (not known to me) on the production of lung edema after intravenous epinephrin injections in rabbits. They performed six experiments, and show no records of pressure changes.

Berge<sup>51</sup> noted repeated pulmonary edema crises following subcutaneous injection of physiologic sodium chlorid solution in an arteriosclerotic individual who was afflicted with Bright's disease and an aortic insufficiency. There was no cutaneous edema at any time. Death occurred some time later in uremic coma with Cheyne-Stokes respiration.

Hamburger,<sup>52</sup> took the ascitic fluid from a patient, aged 9 years, and injected it into a calf. There was a marked increase in the lymph flow. On heating the fluid two hours at 56 C this lymphagocic action was destroyed. The micrococci isolated from the fluid also had a lymphagocic action. Fluid flowed from the nose of the calf, and there was an hydropic swelling of the interstitial tissue of the lung. He cites the presence of lymphagogues in cases of cardiac dropsy (Lepine), inflammatory hydrops (Talma), uremics (Starling), and in chronic hemorrhagic nephritics with edema. His view is that with hindrance of outflow of blood certain products accumulate in the capillaries and

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48 Teissier and Guinard. *Nouvelles recherches experiment sur la pathogen de l'oedeme aigu du poumon*, J de Physiol et de path gener **3** 42, 1901.

49 Bouchard and Claude. *Recherches exp sur l'adrenaline*, Compt rend de seances de l'Acad D S **135** 928, 1902.

50 Josue. Not located.

51 Berge. *Oedeme pulmonaire provoque par l'injection souscutanee de serum artificiel*, Bull et Mem de la Soc med d hôp de Par, 3d Series **20** 1349, 1903.

52 Hamburger. *Osmotischer Druck und Ionenlehre* **2** 67, 1904.

stimulate the capillary endothelium to greater lymph production. He speaks of autogenous lymphagogues. The vessel walls may also have an increased permeability.

Meltzer<sup>53</sup> observed pulmonary edema in rabbits after a large dose of epinephrin. The left ventricle cannot force out all of its blood because the systemic vessels are constricted. The right ventricle, stimulated by the epinephrin, unloads with increased energy the blood which the contracting vessels drove into it. The combination produces lung edema.

Welch,<sup>54</sup> at Meltzer's request, restates his views on lung edema, twenty-five years after his original contribution. Welch reiterates that lung edema occurs following a passive hyperemia, and that the important factor is passive congestion in the pulmonary artery. This is obtained by producing "a disproportion between the working power of the left ventricle and of the right ventricle of such a character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." He maintains that Mayer, Grossmann and Lowit have confirmed his work. A weak pulse is not necessary. The relation between the forces of each ventricle is the essential thing. An edematous lung can be pale. Osmotic pressure, alterations in capillary endothelium and interference with lymph absorption are conceivably not sufficient factors alone to be primary causes of acute general edema of the lungs. He agrees with Sahl<sup>55</sup> in that "a larger number of cases of pulmonary edema are referable to inflammatory changes in the vascular walls than is generally supposed." His opinion is based on systematic bacteriologic examinations at the Johns Hopkins Hospital necropsies.

Sahl<sup>55</sup>, also at Meltzer's request, still states that Welch's theory is untenable, and underscores the inflammatory type as the main one met in practice.

Jores<sup>56</sup> produced lung edema in four minutes in one lobe of a dog's lung by letting that lobe inhale carbonic acid through a tube. The localized effect rules out circulatory disturbance due to the heart. He quotes Mares as saying that the edema is not due to the acid but to the mechanical asphyxia which disturbs the vessel walls. A tube without gas in it produces the same effect. If a large tube is used no edema results. It is easy to obtain edema, a localized edema, if a tube is inserted into a bronchiole. Reflex respiratory standstills or ballooning a bronchus were negative. Jores concludes that the presence of an

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53 Meltzer. *Edema*, *Am Med* 8 195, 1904.

54 Welch. See Ref 11, also Ref 53.

55 Sahl. See Ref 15, also Ref 53.

56 Jores. *Ueber experimentelles, neurotisches Lungenodem*, *Deutsch Arch f klin Med* 87 389, 1906.

irritating foreign body to the mucous membrane of the smaller bronchioles is the cause of a sharply localized lung edema in a very short time. It is not a stasis edema, nor is it toxic or infectious, therefore it must be of neuropathic origin. He stimulated the external surface of the lung faradically for ten minutes. The rabbit remained quiet. Edema followed. Similar results were obtained with dogs. He believes that the electrical stimulation produces a local vasodilation. With the same technic, including section of the right vagus, done three weeks before the experiment, an edema was obtained. Section of the sympathetics and right vagus was attempted, but the animals died of pneumonia in five days. He concludes that disturbance of the gas exchange per second has no influence on the origin of lung edema.

Heinz,<sup>57</sup> in a general discussion of lung edema, notes its occurrence especially with cardiac poisons. The type found is an acute, general, pulmonary edema. He directs attention to the fact that lung edema may easily be simulated by excess secretion of the bronchotracheal system. Therefore, one must be cautious when making a diagnosis by a transudate emanating either from a tracheotomy opening or the mouth. He found that perfusion of a heart-lung preparation (rabbit) with a solution containing three parts Ringer's solution and one part blood usually resulted in acute, general edema in thirty minutes. Heinz also produced an epinephrin pulmonary edema. In gassing with chlorine, bromine, ammonia, hydrochloric acid, hydrobromic acid, hydrofluoric acid and nitric acid there is a preliminary expiratory standstill.

Josue and Bloch,<sup>58</sup> showed lung edema in rabbits after intravenous injections of epinephrin. They were confirmed by Bouchard and Claude.

Chemery<sup>59</sup> reviewed the subject of lung edema in his thesis, but presented no original experiments. He favors a mixed theory of lung edema causation, first, hypertension, second, chlorine retention and third, a nervous element.

Emerson<sup>60</sup> gave epinephrin intravenously to cats. This produced left ventricular dilatation, which is accompanied by mitral regurgitation. This in turn leads to acute congestion of the lungs, dilatation and failure of the right heart. Stagnation in the small circulation produces edema. Artificial respiration in an advanced stage of edema is of benefit.

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<sup>57</sup> Heinz. *Handb. d. exper. Path. u. Pharmakol.* 2:525, 1906.

<sup>58</sup> Josue and Bloch. *Action hypertensive de la couche corticale des capsules surrenales*, *Semaine méd.* 1907, No. 25.

<sup>59</sup> Chemery. *Contribut. a l'étude de l'oedème aigu du poumon et de sa pathogenie en particulier*, *Thèse*, Paris, 1908.

<sup>60</sup> Emerson. *Artificial Respiration in the Treatment of Lung Edema*, *Arch. Int. Med.* 3:368 (March) 1909.

Miller and Matthews<sup>61</sup> studied the effects of nitric oxid, ammonia, illuminating gas, epinephrin and hydrocyanic acid. They also produced artificial mitral stenosis. Dogs and rabbits were given ether under artificial respiration. Carotid and pulmonary artery pressures were taken. Edema was obtained with nitric oxid. Both pressures fell. Irritation of the epithelium or underlying vessels is the important factor. Ammonia vapor produced the same results as nitric oxid. Carbon monoxid produced no pulmonary edema. A slight fall in carotid pressure was accompanied by a slight rise or stationary pulmonary artery pressure. No edema was obtained with hydrocyanic acid. The lung artery pressure was unchanged or lowered gradually. Lugol's solution produced a temporary rise in the carotid, then a fall, while the pulmonary artery pressure rose. The right heart was dilated, while the left heart was unchanged. Edema was produced. They confirm Lowit's observation that acetic ether, given intravenously, results in pulmonary edema in dogs. This substance produces a temporary fall in the carotid pressure. The right heart is dilated, while the left heart never is dilated. A marked bradycardia precedes cardiac standstill. A small dose always gave a decided rise in the pulmonary artery pressure, while a large dose occasionally was negative on the latter pressure, although edema was present. They say a rise in the latter pressure occurs after the edema appears. They call attention to Silbermann's work<sup>61a</sup> that capillary thrombosis may readily be induced by toxic agents, and that the lung capillaries, because of small caliber and low blood pressure may be especially prone to thrombosis, which may be responsible for the rise in the pressure of the lung artery. Intravenous injections of epinephrin were negative unless the thoracic aorta was ligated. Then a marked pulmonary edema followed. Stasis results because the left ventricle is unable to empty itself completely. If a marked mitral stenosis is produced, an edema follows. Acetic ether edema is usually associated with evidence of disproportion between the two sides of the heart, but they feel that the mechanical factors are not responsible for the edema.

Bokarius<sup>62</sup> reviews the subject briefly, and supports Welch on the basis of pathologic diagnoses in selected clinical cases out of 1,200 submitted. He chose clearly cut cases of lung edema with cardiac weakness but not valvular disease or lung changes other than the edema.

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61 Miller and Matthews. A Study of the Mechanical Factors in Experimental Acute Pulmonary Edema, *Arch Int Med* 4 356 (Sept) 1909

61a Silbermann. *Virchows Arch* 117 288, 1889

62 Bokarius. Zur Entstehung des Lungenödems, *Viertelj f g Med* 41 307, 1911



Knowlton and Starling,<sup>63</sup> in revising the technic of the isolated mammalian heart-lung preparation method, eliminate the mercury because enough of it is taken up by the perfusion fluid to have a deleterious effect. The lung capillaries suffer first, and after a somewhat variable period pulmonary edema usually terminates the experiment. With this defect corrected, they noted that when the point of maximum cardiac output is reached the venous pressure rises rapidly, and that if it is maintained pulmonary edema always appears.

Klemensiewicz<sup>64</sup> noted that with fresh serum no edema occurs in the isolated heart-lung preparation. If old serum, or too dilute serum, or isotonic solutions are used, then lung edema occurs easily, whether the lungs are artificially respired or not. Ligation of vessels at the hilus injures the vessels, and on release of the ligature edema sets in regularly (rabbit).

Kotowschtschikow<sup>65</sup> reviews lung edema in a very able manner. He performed about seventy-seven experiments on dogs. They were given morphin and chloroform. If an open thorax operation was performed, curare was given. He obturated the heart chambers, infused, ligated the aorta, and sent emboli into the lung capillaries. Obturation of the left auricle was the most successful procedure in producing edema. The pulmonary artery pressure rose, the carotid pressure fell, the pulse remained about constant, while the right ventricular pressure rose markedly. A lycopodium seed suspension as emboli produced edema in two experiments. A marked hydremia usually produced edema. Hindrance of pulmonary outflow is essential. Silver nitrate was given in thirty-six experiments. Thirty-four of the animals showed lung edema. These could be divided into two groups. First, those in which mechanical factors helped produce stasis, second, those in which no such factors appeared. In most cases, the right ventricular pressure rose, the left auricular and aortic pressures fell. There was usually asynergy of the cardiac chambers, with the left heart weaker. Ether injection produced lung edema. No mechanical changes appeared, therefore vessel wall injury is hypothecated by the author. Methyl salicylate produced lung edema in each of six experiments. The right ventricular pressure can be high but need not be. There is no change in the carotid pressure. Muscarin produced no changes. Lugol's solution was used, but the author does not draw any conclu-

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63 Knowlton and Starling. Temperature and Blood Pressure Variations on Isolated Mammalian Heart-Lung Preparation, *J Physiol* **44** 207, 1912.

64 Klemensiewicz. Das Lungenodem, Krehl and Marchand's *Handb d Allg Pathologie*, Part 1 **2** 424, 1912.

65 Kotowschtschikow. Zur Frage nach den Veränderungen der Herzthätigkeit und des Blutkreislaufs bei acutem Lungenodem, *Ztschr f exper Path u Therap* **13** 400, 1913.

sions from a few experiments. He attempted to confirm Jores, but was unable to do so. He believes that the most common cause of lung edema is a toxic one, and that less often mechanical factors are operative. In the latter cases the pulmonary artery pressure is higher, the right ventricle works better and the systemic blood pressure is lower. The mechanism of toxic edema experimentally induced may be increased permeability of the lung capillary walls, or capillary thrombosis.

Biedl<sup>66</sup> notes that an intravenous lethal dose of epinephrin causes a lung edema in rabbits which is a stasis edema.

Kraus<sup>67</sup> performed his experiments on intact rabbits and on cats with open thorax. The latter had their lung volume, pulmonary artery, venous and carotid pressures recorded. Urethane was given, but no morphin. The roentgen ray shows a larger heart after salt is injected intravenously in rabbits. The carotid pressure rises, the lung volume increases, then decreases. A second injection produces no increase in the size of the heart. Injection of salt solution plus double vagotomy produced an acute pulmonary edema immediately. This occurs in cats and rabbits, whether the thorax is open or not. Epinephrin aids the onset. His electrocardiographic findings are recorded elsewhere, he says, in a journal not stated. He interprets the roentgenograms as showing a diminished air capacity and hyperemia in the edematous lungs.

Evans and Starling<sup>68</sup> used a method in their isolated heart-lung preparations which diminished the tendency for pulmonary edema occurring so often. After some hours there is always more or less edema. Fuhner and Starling,<sup>69</sup> using the same method, showed that with a rise in venous pressure, the heart volume increases, and there is a rise in the lung artery, left auricle and aortic pressures. On the other hand, the venous pressure shows only small differences during wide alterations in the aortic pressure. If the left ventricle fails, and the right heart beats strongly, then the pulmonary pressure rises. Patterson and Starling<sup>70</sup> state that accumulation of blood in the right heart, with fair response of the latter, may cause pulmonary edema. Maximum cardiac efficiency, persisted in too long, tends to give rise to pulmonary edema. Patterson, Piper and Starling<sup>71</sup> conclude that within wide limits cardiac output is determined by and equal to the

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66 Biedl. *Innere Sekretion*, Berlin, Ed 2, 1 522, 1913.

67 Kraus. *Ueber Lungenödem*, *Ztschr f exper Path u Therap* 14 402, 1913.

68 Evans and Starling. *Oxidation in Lungs and Isolated Heart-Lung Preparation*, *J Physiol* 46 415, 1913.

69 Fuhner and Starling. *Pulmonary Circulation*, *J Physiol* 47 290, 1913.

70 Patterson and Starling. *J Physiol* 48 357, 1914.

71 Patterson, Piper and Starling. *J Physiol* 48 497, 1914.

inflow into the right auricle A heart weighing 50 gm puts out as much blood as it receives, whether this be 200 cc or 2,000 cc per minute

Weber<sup>72</sup> criticizes Grossmann's data obtained with muscarin Weber studied experimental asthma and innervation of the bronchial muscles No mention is made of edema onset in his experimental lungs

Magnus, Sorgdrager and Storm van Leeuwen<sup>73</sup> return to Magnus' problem of 1902, concerning the impermeability of the alveolar epithelium to ammonia gas Hober, 1912, showed the appearance of ammonium hydroxid in the lungs, after ammonia was put into the pulmonary artery, and when pulmonary edema was present Magnus<sup>74</sup> never obtained lung edema when ammonia was put into the circulation Magnus et al repeated and confirmed Magnus' 1902 experiments They showed that with ammonia inhalation the greatest absorption and injury takes place via the tracheal and bronchial mucous membranes, and that the alveolar epithelium is relatively impermeable in rabbits even with ammonia percentages of 5.8 to 8.5 They also used the isolated lung preparation (Brodie's method) Cats and rabbits were etherized An arterial pressure of from 35 to 38 mm was maintained No lung edema appeared in normal lungs during the duration of the experiments—three hours In eleven experiments, from 0.015 to 0.017 per cent of ammonia was placed in the blood The drug seeps through the pleura but does not appear in the expired air In one experiment the lung was kept bloodless a short time, while in another chloroform had been administered and fluid appeared in the trachea The expired air contained ammonia in both experiments The plethysmograph showed absence of bronchial spasm Five experiments were done with increased amounts of ammonia in the blood, from 0.027 to 0.045 per cent Lung edema followed and ammonia appeared in the expired air Therefore, they say, the alveolar epithelium is injured With the onset of lung edema, the respiratory excursions become smaller and finally stop The normal alveolar epithelium is impermeable to ammonia, while that of the pathologic lung is not McGuigan's paper<sup>75</sup> contains references on ammonia absorption by the lungs A few of the experiments that he cites seem to have caused pulmonary edema

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72 Weber Experimental Asthma and Innervation of the Bronchial Muscles, *Arch f Anat u Physiol*, 1914, p 63

73 Magnus, Sorgdrager, and Storm van Leeuwen Ueber die Undurchgangigkeit der Lunge fur Ammoniak, *Arch f g Physiol* 155 275, 1914

74 Magnus Schmiedeburg's *Arch* 48 100, 1902

75 McGuigan The Absorption and Excretion of Ammonia by the Lungs, *J Pharm & Exper Therap* 4 453, 1913

Modrakowski<sup>76</sup> is the first investigator of experimental lung edema per se in surviving mammalian lungs. He employed the Brodie apparatus. More than fifty cat preparations were perfused with defibrinated blood or physiologic sodium chlorid solution containing from two thirds to three fourths defibrinated blood. He postulated the presence of edema when the following combination was present: a transudate in the trachea, no maximal pulmonary expansion, and when the lung did not readily collapse. He produced an acute lung edema in five minutes, and thereupon the experiment was stopped at once. In his first series, the pulmonary artery pressure was raised above normal, and considerably above, while the venous outflow was unhindered. Edema did not occur in this series. In the second series, the lung outflow was hindered by raising the pulmonary vein pressure. Lung edema was produced when the pulmonary artery and pulmonary vein pressures were raised high enough. Venous stasis alone, with venous pressure below 35 mm, is negative. Lung edema arises when with a pulmonary artery pressure of not less than 35 mm Hg the venous outflow is so obstructed that their difference drops to 8 mm. If the epithelium or vessel walls are injured, then the permeability of the lung tissue becomes greater. In a hepatized lung (right lower) with the other lobes postpneumonic, edema was produced by only increasing the pulmonary artery pressure. In this experiment there was no venous stasis present. Ammonia in the blood produces edema with either normal or high pulmonary artery pressure, and when there is no obstruction to pulmonary vein outflow.

Staehelin<sup>77</sup> reported seeing many cases of phosgene poisoning all of which showed a general bronchitis and bronchiolitis with lung edema. Fever was present in all the cases. Microscopic examination of one case gave the following data— inflammation of bronchi, marked desquamation of alveolar epithelium, numerous alveoli filled with fluid, and thrombi in many pulmonary arterioles. He believes that there need be no assumption of bacterial invasion to explain the phosgene effects. Hydrochloric acid arises from carbonyl chlorid in a moist environment, and injures the epithelium.

Roos<sup>78</sup> presents five cases of phosgene poisoning, some covering a period of six years, with detailed description of signs, diagnosis, treatment and postmortem examination. This report is unique in that a real attempt was made to centralize attention on cause and result. At venesection it was noticed that the blood coagulated very quickly. Notable observations by Roos are the decreased cardiac energy in all

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<sup>76</sup> Modrakowski. Experimental Lung Edema in Surviving Mammalian Lungs, *Arch f d g Physiol* **158** 527, 1914.

<sup>77</sup> Staehelin. Contrib Ed Handb d Inn Med **2** 287, 302, 315, 1914.

<sup>78</sup> Roos. Phosgenvergiftungen, Thesis in Viertelj f ger Med **47** 67, 1914.

the cases, the lung changes, the heart picture and the negative spectroscopic and chemical examinations of the blood. The roentgenogram showed cardiac dilatation in two cases. Summarizing his data, we have acute dilatation, severe cough, after a few hours marked dyspnea, nearly asphyxial, albuminuria, stasis polycythemia and a marked leukocytosis, pneumonic foci, with desquamation of alveolar epithelium and leukocytic infiltration, subpleural petechial hemorrhages, acute bronchiolitis, multiple thrombi of lung arteries, increase in the amount of fibrin and multiple thrombi in brain, lungs and intestinal vessels.

Kuno<sup>79</sup> studied the dog's heart-lung preparation. The pressure in the left auricle rises steadily with increase in venous inflow. The pulmonary artery pressure always rises when there is increase in the venous inflow beyond a certain point.

Evans and Matsuoka<sup>80</sup> deduct from their isolated heart-lung preparation experiments, that lung edema comes on with ease at high pressures (apparently above 170 mm) in the aorta. Knowlton and Starling<sup>81</sup> state that increase in cardiac output runs parallel with increased aortic pressure until a maximum output is reached. Then the output falls rapidly. The venous pressure rises before there is any falling off in total output of the heart. Markwalder and Starling<sup>82</sup> find that the cardiac output is markedly independent of other factors. The previous data did not consider the coronary circulation, they insist.

Matsuoka<sup>83</sup> discusses the pathology of obstructive lung edema as obtained in the Starling heart-lung preparation. His English is ambiguous, and there seem to be too many conclusions for the amount of data presented. Defibrinated blood with leech extract was the perfusing fluid used. The cardiac output was taken as a measure of venous inflow. When there is a relatively low arterial pressure, a very large venous inflow must be maintained for some time to produce edema. It is possible to increase the venous inflow without causing edema when a high arterial pressure prevails. Obstruction of the aortic root produces an edema with a relatively small venous inflow. The pulmonary artery pressure is raised in such a case. The blood pressure in the pulmonary artery rises with a coordinate rise of the inferior vena cava. During edema, the heart output may be reduced to a minimum, the blood content of the heart may be increased to a maximum, the pressures of the pulmonary artery, inferior vena cava, and right auricle may be increased to a maximum, all quite indepen-

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79 Kuno. Pulmonary Circulation, *J Physiol* **50** 140, 1915

80 Evans and Matsuoka. Gaseous Metabolism and Efficiency of the Mammalian Heart, *J Physiol* **49** 378, 1915

81 Knowlton and Starling. *J Physiol* **44** 206, 1912

82 Markwalder and Starling. *J Physiol* **48** 348, 1914

83 Matsuoka. Pathology of Obstructive Edema of the Lung. Heart-Lung Preparation, *J Path & Bact* **20** 53, 1915

dently of the height of arterial pressure and amount of venous inflow. With a heart weighing 45 gm the pulmonary artery pressure must be over 40 mm Hg and be accompanied by venous obstruction so that lung edema may arise. Edema never occurs in healthy dogs' lungs when the pulmonary artery pressure is lower than 40 mm Hg. The principal factors in transudation are the high pressure in the pulmonary circuit and the excessive passive dilatation of the lung capillaries. The gaseous metabolism and the energy consumption of the heart decrease in obstructive lung edema. The heart always dilates before the occurrence of edema.

Martin Fischer<sup>84</sup> discusses lung edema briefly in his thesis, and mentions a few experiments of his own. An edema results whenever the oxygen supply to the lung parenchyma is interfered with sufficiently. This can be done effectively by ligation of nutrient vessels, directly or indirectly, via interference in the systemic circulation, such as compression of left ventricle or aortic root. Ligations to a point immediately below the subclavian artery lead to edema, because the bronchial arteries leave the aorta just below the left subclavian. Ligation below the bronchial arteries is negative. The lack of oxygen leads to accumulation of acids in the tissues. Clinically, pulmonary edema occurs more frequently in nephritis than in heart disease because toxic bodies injure the lung parenchyma as well as other tissue. It is easy to produce edema in the excised lung because there is an interference with the normal oxygen supply. Fisher took sheep's lungs and permitted water or M/6 (0.975 per cent) sodium chlorid solution to trickle into the pulmonary arteries, producing an intense edema. A lung weighing 500 gm will take up several liters in an hour. Two periods can be designated. During the first period there is no fluid in the trachea. Later, the pleural surface is moist, and a bloody, frothy fluid emerges from the trachea. Although the veins are not ligated, no fluid emerges. The longer the lungs have been out of the animal the more quickly do these signs of pulmonary edema appear. Sodium citrate and sodium sulphate are more effective than sodium chlorid. In other words, the salts which dehydrate various protein colloids best are most effective, and therefore, the colloid theory of water absorption applies here. More water is held because acids are produced in the tissues. The tissue colloids have their capacity for water increased by the acids present.

Schafer<sup>85</sup> gives an excellent report on chlorin gas poisoning. He commends Lehmann's work. Cats, rabbits and dogs were anesthetized, and then gassed. Ringer's solution saturated with chlorin injected

<sup>84</sup> Fischer. *Edema and Nephritis*, Ed 2, 1915, p 233

<sup>85</sup> Schäfer. *On the Immediate Effects of the Inhalation of Chlorin Gas*, Brit M J 2 245, 1915

intravenously produced a slight fall in blood pressure and a slight increase in the depth of respiration. Inhalation (1 per cent chlorin) had no immediate special effect on blood pressure or respiration, but ultimately the blood pressure fell, the respirations became deep and convulsive prior to complete arrest, and the pulse was slowed. Substitution of air produced recovery with higher blood pressure. The chlorin cannot be carried to the tissues in a free state. The short exposures show changes only in the lungs. They are congested, more solid and are slightly crepitant. He believes that fatality may be due to obstruction of pulmonary vessels. Experiments with surviving lungs and with lungs in the intact animal show a bronchiolar dilatation during gassing. This was done by catching the air escaping from the lung surface through needle holes. Chlorinated Ringer's solution perfused into the pulmonary artery produces marked constriction. Schafer presents microscopic plates of edema, interstitial and alveolar, and of capillary engorgement. Presumably, the edema is secondary to the vascular obstruction. Mucus does not play an important part (excluded by atropin). Bromin vapor is less deleterious.

Hill<sup>86</sup> discusses gas poisoning especially with chlorin. The respiratory epithelium and pulmonary capillaries are injured, and the osmotic pressure of the damaged tissue is raised, producing the edema. Albuminuria is conceivably due to decreased oxygen supply to the kidney. Barcroft, he says, has shown the presence of an increased acidity of the blood. The edematous fluid produced may drown the animal. In weak concentrations, chlorin does not produce death by stasis in pulmonary vessels. When lungs were artificially respired and manipulated so that a chlorin-air mixture could be sent into one lung leaving the other airless, then an edema arose in the first lung, followed by asphyxia and failure of circulation. Recovery was rapid if air was sent into the normal lung. Kuno and Hill, he reports, administered chlorin in heart-lung preparations. They obtained congestion and edema, while the blood became more and more venous. The cardiac output was diminished. A microscopic description is given. Strong concentrations of chlorin gas causes contraction of the bronchiolar musculature. Pneumonia and bronchitis are almost invariable sequels.

Matsuoka<sup>87</sup> believes that the lung edema of beri beri is a characteristic feature of the disease, and is essentially an obstructive edema. This citation is of value in that Yamagiva, the noted pathologist, says that this lung edema is due to the contraction of pulmonary arterioles and bronchioles.

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86 Hill. Gas Poisoning, Brit M J 2 801, 1915

87 Matsuoka. Lung Edema in Beriberi, J Path & Bact 20 191, 1916

Slovtzov, Chernewski and Xenophontov,<sup>88</sup> in a study on the chlorine content of the air as affecting oxidative functions and gaseous exchange, state that there is a diminished oxidation lasting for some hours

Slovtzov<sup>89</sup> finds that in rabbits chlorine inhalation increases the coagulation time, diminishes the alkalinity, destroys the leukocytes, increases the red blood corpuscles, and increases the thrombin content in pulmonary tissue

Slovtzov<sup>90</sup> describes the clinical signs, pathology and physical findings in cases of phosgene poisoning in man, horses, guinea-pigs, rats and dogs. The acute poisoning resembles that induced by chlorine, although it is milder. Most noticeable are the lung changes, myocarditis, nervous depression and alterations in the blood. The red cells are disrupted, there is increased coagulation and viscosity and decreased alkalinity

Lucherini<sup>91</sup> gives a graphic account of gas poisoning from the war zone

Auer and Gates<sup>92</sup> continue their study of fulminant pulmonary edema induced by intratracheal administration of epinephrin. They had previously found the onset more rapid in the vagotomized rabbit. Intratracheal administration of epinephrin in this series of rabbits gave them the following results. In twenty-seven experiments, marked edema occurred in twenty-one with vagi cut. In sixteen with vagi intact, slight edema was present. Direct observation (six out of seven experiments) of the heart showed that epinephrin induced alternating strong and weak beats of the left ventricle with halving of its rate. The dilatation of the left auricle was often tremendous. Artificial respiration has a restraining influence on the onset of lung edema. Tracheal stenosis facilitates edema production. Atropin exerts a protective action. Auer and Gates favor Welch's view of the disproportionate activity of the ventricles which in their experiments is induced by adrenalin.

Kuno<sup>93</sup> observes that when the blood used for the heart-lung preparation (dogs) is somewhat old, then the lungs gradually pass into an edematous condition. Postulating that the pulmonary circulation in

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88 Slovtzov, Chernewski and Xenophontov. Chlorine on Oxidative Functions and Gas Exchange, *Vratschebnaya Gaz*, 1916, p 23, also *Physiol Abstr* **2**, 621, 1917

89 Slovtzov. Chlorine on Animals, *Arch d Sc Veterinaires*, 1916, p 3, also *Physiol Abstr* **2** 621, 1917

90 Slovtzov. Phosgene Poisoning, *Russk Vrach* **15**.649, 1916

91 Lucherini. Asphyxiating Gases, *Arch farm sper* **22** 429, 1916, also *Chem Abstr* **11**.995, 1917

92 Auer and Gates. Adrenalin Pulmonary Edema, *J Exper M* **26** 201, 1917, *Ibid* **23** 755, 1916

93 Kuno. Amount of Blood in the Lungs, *J Physiol* **51** 154, 1917



edema is very slow, he kept the venous supply to the heart very low in two experiments in which he determined the amount of blood present in the lungs in edema. In normal lungs, the blood was from 88 to 194 per cent of the total blood (equal to 7 per cent of body weight), depending on the velocity of the blood. The edematous lungs contained 234 and 262 per cent of the total blood.

Pellegrino<sup>94</sup> reports histologic researches on the pulmonary alterations following inhalation of bromin.

Kramer<sup>95</sup> describes the effect of chlorin on the lungs, noting among other things thrombosis in lung and heart vessels.

Klotz<sup>96</sup> describes acute death from chlorin poisoning in mice, guinea-pigs and rabbits. Concentrations of from 1, 1,000 to 1, 10,000 are lethal in from three minutes to one half hour usually. A post-mortem examination shows hyperemic lungs, with little fluid blood in congested areas. The blood coagulates within the dilated pulmonary capillaries. The unusually rapid coagulation may be the result of the intense edema whereby the blood constituents within the vessels are greatly altered. Human blood in 1, 1,000 concentration coagulates in fifteen seconds, while stronger concentrations reduce this time. Hake<sup>97</sup> found that diluted blood yielded a colorless filtrate after chlorin gas was bubbled through it. A practically colorless precipitate was formed at the same time. The iron found gave the tests for the ferric salts.

Kruglevsky, Boldereff, Neporsky, Neiding, Sereisky and Gokh<sup>98</sup> present a series of papers on acute edema produced in gas poisoning. They discuss treatment, effect on vegetative nervous system, nervous symptoms, psychic symptoms and the intravenous oxygen treatment.

Meek<sup>99</sup> produced lung edema by intravenous injection of collargol. The fluid practically poured from the trachea. A microscopic study showed that it was purely an obstructive edema, with emboli in the pulmonary and coronary circulations.

General treatises on lung edema of importance are those by Ziegler,<sup>100</sup> Staehelin,<sup>77</sup> Heinz,<sup>57</sup> Kunkel<sup>39</sup> and Klemensiewicz.<sup>64</sup>

94 Pellegrino. Histological Researches on the Pulmonary Alterations Following the Inhalation of Bromine, *Arch farm sper.* **24** 58, 1917.

95 Kramer. Chlorin Poisoning, *Viertelj f ger Med* **53** 181, 1917, also *Chem Abstr* **12** 1918, also *Physiol Abstr* **2** 528, 1917.

96 Klotz. Acute Death from Chlorin Poisoning, *J Lab & Clin Med* **2** 889, 1917.

97 Hake. Chlorin on the Blood, *Lancet* **2** 86, 1915.

98 Kruglevsky, Boldereff, Neporsky, Neiding, Sereisky and Gokh. Acute Edema of the Lungs and Various Phases of Gas Poisoning, *Russk Vrach* **16** 385, 1917, also *Physiol Abstr* **3** 61, 1918.

99 Meek. Personal Communication, 1918.

100 Ziegler. *Lehrb d allg Path* **2** 765, 1906.

Cushny<sup>101</sup> notes the frequent occurrence of lung edema in cats and rabbits after poisoning with pilocarpin. This has also occurred in man. Pilocarpin, in toxic amounts, contracts the bronchi, retarding the movement of the air, retards the heart, slowing the circulation through the lungs, and has a tendency to cause convulsive movements, accompanied by rapid and labored respiration, which eventually becomes slow and weak. Asphyxia follows.

#### STATUS OF THE PROBLEM AFTER NOVEMBER, 1918

Shortly after the armistice was signed November 11, permission to various war department groups of investigators was granted allowing them to publish their observations on experimentally induced conditions in which pulmonary edema occurred as a prominent symptom. However, there has as yet been no comprehensive experimental study submitted concerning the cause and treatment of the edema. Barbour and Williams<sup>102</sup> report the effects of chlorin on isolated bronchi and pulmonary vessels. Winternitz and Lambert<sup>103</sup> discuss the pathology of lungs obtained from gassed dogs, with emphasis on the edema as a cause of death. Underhill<sup>104</sup> delivered an excellent Harvey lecture on the physiology and experimental treatment of poisoning with the lethal war gases in which considerable experimental data were summarized, but the data were not submitted.

#### SUGGESTIVE METHODS FOR THE STUDY OF EXPERIMENTAL LUNG EDEMA

The detailed investigation of lung edema caused by toxic gases in the medical section of the Chemical Warfare Service directed the attention of the group at the University of Wisconsin Medical School laboratories to the following points in relation to the onset and cause of the edema: Whether there is an increase or decrease or both in (1) the blood volume, (2) red and white cell count, (3) hemoglobin percentage, (4) amount of fibrin, (5) thrombin, (6) freezing point of blood, (7) presence of lymphagogues in the blood stream, (8) spectroscopic examination of the blood, (9) chemical examination of the blood, (10) agglutination, (11) viscosity of the blood, (12) coagulation time, (13) blood counts from the right and left hearts, (14) the alkali reserve, (15) the  $p_H$  value of the blood, (16) histologic changes

101 Cushny Textbook on Pharmacology, 1918

102 Barbour and Williams The Effects of Chlorin on Isolated Bronchi and Pulmonary Vessels, *J Pharmacol & Exper Therap* **14** 47, 1919

103 Winternitz and Lambert Edema of the Lungs as a Cause of Death, *J Exper M* **29** 537, 1919

104 Underhill The Physiology and Experimental Treatment of Poisoning with the Lethal War Gases, *Arch Int Med* **23** 753 (June) 1919

in the bone marrow In addition to these, the following topics require investigation (17) the cause of polycythemia, whether it is due to decreased blood volume or to decreased oxygen supply, (18) roentgen-ray studies of the heart and lungs, (19) the first sign of the onset of edema, or a simultaneous factor occurring at the time of edema onset, (20) the pathology at various stages up to the time of death, (21) the vital capacity of the lungs, (22) wet and dry weights of the lungs, (23) response to increased oxygen or carbon dioxide administration, especially from time of gassing up to the onset of edema, (24) pressures in the following vessels and heart chambers — carotid, aorta, pulmonary vein, pulmonary artery, jugular vein, right ventricle, left ventricle, brachial artery, (25) wet and dry weights of tissues other than the lungs, as, for instance, muscle, to account partially for loss in blood volume, (26) direct effect of toxic substance as gas or chemical on the isolated or excised heart by perfusion, (27) direct effect on a surviving lung and such isolated pulmonary structures as arteries, veins and bronchi, (28) the cause of dyspnea, (29) the respiratory quotient, (30) the respiratory minute volume, (31) the picture produced by gassing one lung or lobe, (32) the presence of bronchiolar spasm

Following the discovery of the cause of edema, one expects that the treatment of the condition could be followed out along suggestive leads However, under the stress of the war situation, the study of treatment was instituted practically simultaneously with the study of the cause of toxic gas edema These measures, briefly summarized were the effect of (1) bleeding, (2) infusions of physiologic sodium chlorid solution, glucose, acacia and mixtures of these, (3) morphin, (4) atropin, (5) the digitalis series and other cardiac drugs, (6) oxygen—by vein, abdomen, etc, attempts at extrapulmonic respiration, (7) neutralization of chemical inhalants in the first stage of poisoning, (8) neutralization of gas products in the respiratory epithelium before injury to the cell has advanced very much, (9) possibility of regeneration of respiratory epithelium by drugs or chemicals, (10) changing the content of the blood so as to overcome the biochemic changes extravascular to the lung capillaries, (11) control of the alkali reserve, (12) maintenance of normal body temperature, etc, etc

#### SUMMARY

A survey of the literature shows that the methods for production of edema fall into a few categories The first method tried was the experimental production of pulmonary emboli by the use of fat droplets, lycopodium seeds, etc (Virchow, Klotz) The edema resulting from pulmonary emboli may be explained in several ways It may

arise because there is a diminished blood supply in the lung nutrient vessels via the aorta, due to the damming back of the blood, or because the right heart continues its pumping action against the emboli obstructions, increasing thereby the permeability of the turgid pulmonary capillaries. Then, again, in the diminished nutritional supply of the heart, there may result a disproportionate activity of the cardiac chambers with the left weaker than the right.

A group of methods can be gathered under the caption "Injury to Pulmonary Capillaries," either from within the vessels or from without. The blood flowing within the vessels may be altered, for example, diluted, as in Cohnheim's and Lichtheim's hydremic plethora animals, or in perfusion of isolated heart-lung preparations (Jacob, Evans, Lovatt, etc.), a collapse in the normal permeability of the lung capillaries results, with the escape of fluid into the extracapillary space, rupturing of the alveoli, and finally filling of the air spaces. The blood may be concentrated, resulting in an anoxemia. The capillary endothelium may be injured directly with acetic ether (Lowit, Miller and Mathews) administered intravenously, or by ammonia (Magnus et al, Modrakowski). A number of French workers have attempted to produce pulmonary edema by electrical stimulation of the exposed lung and have thought that the results obtained suggested a nervous element. They insist on a reflex dilatation of the lung vessels (Jores, Teissier and Guinard). There seems to be little experimental evidence for this point of view. Another possible cause for the pulmonary injury is the production of acid products in the lung interstitial tissue due to altered blood in the nutrient vessels of the lung (Fischer).

Injury outside of the pulmonary capillaries may result from a destruction of the respiratory epithelium, as, for example, by toxic gases (Lehmann, Pettenkofer, Kockel, Roos, Modrakowski, Schafer, Hill). Fluid would escape into the air spaces due to increased permeability of the alveolar wall resulting from the injury. Another form of injury to the respiratory epithelium might follow bronchiolitic spasm, as in chlorine gas poisoning (Barbour and Williams).

The inflammatory type of pulmonary edema, which Sahlh insisted on as the chief type in man (confirmed by Welch), might be considered as a combination of intravascular and extravascular injury. Hamburger brought proof to show the lymphagogue power of certain bacteria and their products in the blood stream. Pathologic evidence also indicates that bacteria can invade the interstitial pulmonary tissue and induce an edema by altering the physicochemical conditions. It is also evident that injury of the lungs in gassed individuals results in diminished resistance to bacterial invasion.

A great mass of work has been done, initiated by Welch, in showing the onset of pulmonary edema in all conditions in which the

mechanical efficiency of the left ventricle is reduced to a greater extent than that of the right ventricle. The pressures in systemic and pulmonary vessels were recorded to prove this assumption. Welch was the first to show that injury or compression to the left ventricle was followed by a pulmonary edema. Others feel that thrombosis in the left coronary artery might do this. Then, again, the toxic action on the left ventricle of rapid intravenous injections of epinephrin seems to corroborate Welch's assumption (Beidl, Auer and Gates, Meltzer, Bouchard and Claude). Probably, the cardiac disproportion is the cause of the edema of asphyxia, whether agonal or not, or, at least, it is a contributing cause. Some observers feel that the heart is the primary cause of edema in certain types of gas poisoning, indicated by its dilatation and change in venous pressure.

It is conceivable that a pulmonary edema may be the resultant of a group of causes. For example, a toxic substance might injure both lung and heart simultaneously, and as the edematous fluid finds an easy outlet, the heart may be developing an asymmetrical pumping activity and thereby massing the blood on the venous side of the lungs. Or a vicious circle might be produced. A substance might induce edema in the first place by injury to the lung parenchyma. This might result in a concentration of blood, which would in turn reduce its oxygen carrying capacity and result in a decreased efficiency of the heart due to poor nutrition. Finally, this might lead to an increase in blood in the right heart, with a greater seeping of fluid through the dilated pulmonary capillaries into the air spaces.

It would seem that the work which has been done on experimental pulmonary edema indicates that the mechanism of causation of pulmonary edema must be sought for beyond the immediately obvious cause, as, for example, intravenous embolism, intravenous injection of drugs like epinephrin and muscarin and toxic chemicals, such as acetic ether, silver nitrate, collargol, etc., injury to the chambers of the left heart, particularly the ventricle, infusions of large amounts of fluid, with or without vagal section, electrical stimulation of lung tissue directly, inhalation of irrespirable gases and vapors (chlorin, hydrogen sulphid, hydrochloric acid, etc.), ligations and compressions of aortic and pulmonary branches, occlusion of bronchi and bronchioles, alterations in the content or amount of blood, obturation of chambers of the left heart, increasing the venous inflow, overriding the maximum cardiac output, and decreasing the oxygen supply to the lung parenchyma.

# AN INVESTIGATION OF THE SIZE OF THE HEART IN SOLDIERS BY THE TELEROENTGEN METHOD \*

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It is not known with sufficient accuracy whether exertion, such as soldiers undergo in warfare, is accompanied by enlargement of the heart. The present study was undertaken to obtain information on this point. The examinations were made during May, 1919, of soldiers who had seen active service in the American Expeditionary Forces<sup>1</sup>

The men were selected without regard to special criteria by line officers at one of the camps in the vicinity of New York<sup>2</sup>. Infantrymen were chosen or men who had been subjected to an equivalent amount of privation and exertion. In this report are given the results of the study of the size of the heart only. Physical examinations were made and electrocardiograms were taken, but the results of these further studies are reserved for later communications.

The examinations now reported were roentgenographic<sup>3</sup>. The exposures were made with sternum turned to, and parallel with, the plate. The distance from the anticathode of the roentgen-ray tube to the photographic plate was 6 feet. A strip of lead about 100 cm long, 60 mm wide, and about 30 mm thick was laid on the skin over the spines of the vertebrae and secured with adhesive plaster. Two acute angles of lead were similarly secured — one in the suprasternal notch and the other in the infrasternal notch. The target of the roentgen-ray tube was adjusted to the level of the lower angle. Whether correct anteroposterior alignment was obtained, could then be ascertained by examining the plate<sup>4</sup>. The exposures were made in

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1 At the same time similar investigations were carried on by Capt B Smith at U S General Hospital No 9, Lakewood, N J. The results of his examinations are given in a separate communication in this issue of the ARCHIVES OF INTERNAL MEDICINE

2 I desire to express my thanks to Major-General Shanks, Commanding Officer of the Port of Embarkation, Hoboken, for his courtesy in placing these soldiers at my disposal

3 I am indebted to Dr Witherbee, who made the roentgenograms, for his painstaking cooperation

4 Mention is made of this technical detail because the use of this method secures greater accuracy than that which employs a lead strip on the sternum and a ring over the a vertebral spine

the standing position In making studies of this kind, Bardeen<sup>5</sup> made the exposure "during deep but not forced inspiration and with two half second exposures with an intervening half second so as to insure a diastolic outline" The exposures were made by Smith<sup>6</sup> during an inspiration of moderate depth after the subject had taken a deep breath and expired it A method involving deeper breathing than normal has this purpose it frees a larger portion of the cardiac shadow from the shadows of the surrounding viscera, especially the liver, and it permits the drawing of the outline of the cardiac shadow with greater ease It is admitted that there is a disadvantage in the procedure, when the breath is held too long it occasions too great a filling of the heart, the photograph of which is, in consequence, larger than normal A modification of the usual technic was, therefore, introduced in this study No directions for breathing during the exposure were given, the men breathed normally In order that the phase of respiration in which the plate was secured might be known, the following technic was devised

On the plate holder a lead strip was secured to indicate the neutral position of the vertically hanging lever of a Marey tambour tipped with a lead ring The tambour was connected by rubber tubing with a Politzer bag held in position in the right axilla by a binder secured by tying its tails, metal fastenings were, of course, avoided During respiration, the lever swung to one or other side of the neutral line indicated by the lead strip The side to which the lever swung during expiration was indicated on the plate holder by fastening there a lead letter E The exposures were brief, a fraction of a second, perhaps as little as one-tenth second on occasion, so that the image of the lead ring of the lever was sharp When the exposure was longer, or the breathing faster, the trail of the lever, as it swung across the plate, appeared on the plate and showed this fact The lever of the tambour was in view of the operator, so that by observing it the exposure could be made in any phase of breathing The desired information was, accordingly, recorded on the plate The attempt was made to secure the exposures during normal inspiration This succeeded in 140 of 161 instances (I, ?, Table 1)

But to study the effect of normal breathing on the size of the heart, the heart in fifty-six instances was photographed both in inspiration and in expiration Note should be taken of the fact that in many

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<sup>5</sup> Bardeen, C R Determination of the Size of the Heart by Means of the X-Ray, *Am J Anat* 23 423, 1918

<sup>6</sup> Smith, B Teleroentgen Measurements of the Hearts of Normal Soldiers, *Arch Int Med*, this issue, p 522

TABLE 1—DATA AND MEASUREMENTS OF THE HEARTS OF  
THE SOLDIERS EXAMINED

No	Phase Respiration	P	Weight, Kg	Height, Cm	Age, Yrs	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees	Notes
1	I		53	157	21	13 4	13 4	94	38	
2	I ?	+	53	152	29	12 7	13 6	102	37	Wounded
3	I		54	164	40	12 0	13 1	108	46	
4	I	+	54	162	20	11 9	13 3	86	40	
5	I		55	158	29	12 8	14 5	122	42	
6	I	+	56	158	25	13 9	13 9	120	43	
7	I		56	173	24	13 8	15 7	112	42	
8	I		56	171	27	12 3	14 3	103	47	
9	I	+	56	168	22	11 2	13 2	92	47	Gas
10	I		57	160	19	12 3	13 8	109	47	Gas
11	I		57	168	24	12 6	15 0	110	47	
12	N		57	172	26	11 5	14 3	110	51	
13	?		57	165	23	11 2	13 7	100	56	Appendicitis
14	?		58	163	24	12 8	13 7	112	37	Wounded
15	I		58	168	25	11 4	13 2	94	52	
16	I		58	170	25	11 2	13 0	94	49	Gas
17	I		59	175	19	12 5	13 9	122	46	Gas
18	I ?		59	169	21	11 5	12 5	99	49	Bronchitis
19	?		59	166	25	11 5	14 0	108	48	
20	I	+	59	167	23	12 5	14 7	108	43	
21	E		60	172	25	12 7	13 6	100	34	Gas, rheumatism (?), dysentery
22	I		60	174	29	11 3	13 0	98	41	
23	E		60	171	25	12 4	14 2	110	42	
24	I		60	162	23	13 3	14 3	106	36	
25	I		60	164	29	13 3	15 1	109	45	Wounded
26	I		60	183	25	12 5	14 3	101	45	
27	I		60	174	21	10 8	13 0	96	46	
28	?		60	173	23	12 5	13 4	107	45	
29	I		60	170	24	12 5	13 7	104	43	
30	I	+	61	161	27	12 8	13 7	103	39	Wounded
31	I		61	174	24	11 8	12 7	102	35	Wounded, gas
32	I	+	61	168	29	10 5	12 5	92	44	Gas, shell shock
33	I		61	164	25	13 0	13 6	113	41	
34	I	+	61	176	27	11 7	13 8	95	47	Appendicitis
35	I		62	163	24	11 2	13 7	121	48	
36	I		62	166	30	14 2	14 6	124	39	
37	I		62	173	29	11 9	13 9	108	50	Gas
38	I	+	62	171	26	12 3	13 2	98	43	
39	?	+	62	173	25	12 5	14 6	109	44	Gas
40	I		62	170	29	13 0	15 0	105	42	Gas
41	I		63	172	50	12 8	11 8	84	32	Gas
42	I	+	63	163	33	14 0	15 0	109	33	
43	I		63	163	26	13 5	14 2	103	34	Gas, wounded, rheumatism (?)
44	I		63	174	40	13 8	14 0	112	42	Gas
45	?		63	169	21	13 5	14 9	130	44	
46	I		63	167	24	11 8	13 4	101	45	
47	I		63	164	21	12 8	14 0	127	45	
48	I		63	169	28	12 0	14 0	100	51	Shell shock
49	I		63	178	23	12 7	13 5	109	50	
50	I		63	170	23	11 3	13 5	97	48	
51	I	+	63	172	20	10 5	13 1	91	53	

Column 2 gives the phase of respiration in which the exposure is made

Column 3 indicates (+) whether exposures were obtained both in inspiration and expiration

Columns 4, 5 and 6 give the weights, height, and age

Columns 7, 8, 9 and 10 give the transverse diameter, the long diameter, the area of the cardiac shadow and the cardiac angle

Column 11 gives notes of interest



TABLE 1—DATA AND MEASUREMENTS OF THE HEARTS OF THE  
SOLDIERS EXAMINED—(Continued)

No	Phase Respiration	P	Weight, Kg	Height, Cm	Age, Yrs	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Om	Angle, Degrees	Notes
52	I		64	167	30	14 4	14 6	125	36	
53	N		64	164	29	12 0	12 5	83	34	
54	E		64	174	23	12 8	13 5	102	38	Gas
55	E		64	167	31	12 7	13 8	104	38	Wounded
56	N		64	173	24	13 4	14 4	129	47	Gas
57	I	+	64	176	21	12 2	13 5	82	38	
58	I	+	64	167	24	12 5	13 9	100	38	Gas
59	I		64	181	29	11 2	13 5	98	45	
60	I		64	171	26	12 8	14 4	108	43	Trench fever ?
61	I	+	64	168	28	13 2	15 2	131	47	Gas
62	I		65	177	28	14 2	14 8	126	38	
63	I	+	65	175	28	13 3	14 6	119	40	
64	I		65	168	20	12 8	13 4	109	42	Gas
65	E		65	170	20	11 8	14 0	114	47	
66	I		65	176	21	12 8	13 3	112	45	Gas, shell shock
67	I	+	65	164	27	12 3	12 8	96	36	Wounded
68	I		65	172	27	12 8	14 0	111	44	
69	I		65	170	23	12 7	15 3	126	50	
70	E		65	170	20	11 2	13 2	95	48	
71	I	+	66	165	22	11 6	13 4	92	39	
72	I		66	164	27	13 5	15 4	126	40	Gas
73	E		66	182	25	12 2	13 6	101	44	
74	I		66	167	26	12 4	14 6	121	53	
75	I	+	66	179	19	12 3	14 5	108	49	
76	E		66	165	21	12 6	15 1	119	48	
77	I		67	161	25	14 5	14 8	109	30	Gas
78	I		67	173	29	14 6	15 3	124	38	Gas
79	I		67	167	25	13 7	15 2	120	38	
80	I	+	67	176	27	13 7	13 5	92	29	Gas
81	I		67	175	23	12 4	13 9	104	37	Gas
82	I		67	167	26	14 4	15 1	109	35	
83	I		67	175	28	12 4	13 0	95	35	
84	I		67	168	27	14 0	14 6	124	41	
85	I		67	169	23	13 2	13 1	94	32	Gas
86	I		67	170	24	15 0	16 3	137	41	
87	I		68	167	49	13 5	14 0	110	31	
88	E		68	171	24	15 0	15 5	139	39	
89	I		68	171	21	13 4	14 0	111	32	Gas
90	I		68	175	24	12 8	14 1	131	43	
91	I		68	174	18	11 8	12 8	99	36	Gas
92	?		68	170	26	13 8	15 1	118	41	
93	I	+	68	174	20	12 8	14 0	114	47	Gas
94	I		68	175	26	14 0	15 1	118	43	
95	?		68	176	23	12 1	15 4	140	55	Gas
96	I	+	68	178	23	13 0	15 5	140	49	Not in France
97	I		69	175	42	15 7	16 1	132	35	
98	N	+	69	180	26	12 7	13 8	108	35	
99	I	+	69	167	22	12 9	13 5	96	38	Gas
100	I		69	169	26	14 8	15 9	129	37	
101	I		69	174	31	13 8	15 1	122	46	Gas
102	E		69	177	23	12 6	14 1	120	41	
103	I		69	177	25	11 8	13 3	110	48	Gas
104	I	+	69	182	28	12 8	15 0	132	45	Gas, wounded
105	I	+	69	171	30	14 8	15 0	135	41	Gas, wounded
106	I		69	172	26	13 6	15 1	110	42	Gas
107	I	+	69	177	28	12 2	14 3	104	42	
108	I		69	180	28	12 3	13 2	106	49	
109	?		70	174	31	13 5	14 6	112	37	Gas
110	I	+	70	180	30	12 0	13 6	100	40	
111	I		70	171	30	12 8	13 2	95	35	
112	?		70	176	40	15 0	15 0	121	42	
113	I		70	176	29	13 3	14 3	109	36	
114	?		70	170	25	13 9	14 3	120	44	
115	I	+	70	175	24	13 0	14 6	114	40	
116	I ?	+	70	184	27	12 8	14 1	109	46	
117	I		70	175	22	11 8	15 0	109	51	
118	I		70	175	18	13 0	14 0	98	42	

TABLE 1—DATA AND MEASUREMENTS OF THE HEARTS OF THE  
SOLDIERS EXAMINED—(Continued)

No	Phase Respiration	P	Weight, Kg	Height, Cm	Age, Yrs	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Om	Angle, Degrees	Notes
119	I		71	172	22	13 7	15 8	122	35	Gas Dysentery ? Measles
120	E		71	167	26	15 0	16 3	136	35	
121	?		71	169	36	14 0	13 8	121	37	
122	I		71	170	29	14 2	14 4	105	32	
123	I		71	177	34	13 3	15 3	110	42	
124	I	+	71	172	27	14 0	15 7	122	40	
125	I		71	178	23	12 1	14 0	91	45	
126	I		71	172	23	11 3	13 3	91	43	
127	I		72	179	24	12 7	12 4	94	30	Wounded, buried
128	I	+	72	167	24	14 2	14 6	110	37	
129	I		72	174	22	14 0	14 8	134	43	
130	N		72	165	23	12 4	13 6	104	39	
131	I	+	72	178	24	13 0	15 2	124	45	
132	I		72	174	20	12 4	15 1	122	48	
133	I		72	174	29	14 7	15 7	127	42	
134	?		72	177	26	13 4	14 5	123	45	
135	I		72	173	21	12 8	15 3	127	52	
136	I	+	73	173	25	14 5	14 9	110	34	Gas
137	I		73	178	21	14 1	14 8	119	38	
138	I		74	174	28	14 4	15 0	114	35	
139	I	+	74	166	22	14 6	14 1	113	33	
140	I		74	171	24	13 7	14 7	110	34	
141	I		74	172	23	12 3	12 7	80	33	
142	I		74	172	25	13 0	14 3	115	45	
143	I		74	178	27	13 3	16 1	146	46	
144	I		74	186	23	12 7	14 3	96	41	
145	I	+	75	175	25	14 7	15 8	115	33	
146	I	+	75	170	28	13 2	14 4	95	37	
147	I		75	173	25	16 0	16 2	108	21	
148	I	+	75	172	25	12 0	13 2	100	39	
149	I		75	165	27	13 0	14 2	118	45	
150	I		75	175	30	13 2	15 3	114	41	
151	?		75	174	21	12 7	14 4	102	45	
152	N		75	175	24	11 0	14 1	111	56	
153	I	+	76	176	25	14 5	15 3	121	33	Febricula
154	I		77	179	28	12 3	15 0	127	48	Trench fever ?
155	I		77	181	30	12 8	15 9	126	49	
156	E		78	173	24	14 2	14 3	110	28	Gas
157	I		78	170	28	14 3	14 8	107	35	
158	I		83	180	27	14 3	15 8	120	39	Wounded
159	I	+	83	182	21	12 5	14 7	124	44	
160	I		83	179	26	13 8	16 6	127	46	
161	I		86	180	26	13 8	14 7	110	36	

persons expiration is not an active process, but is the release from inspiration. In these cases, the expiratory phase is represented by the neutral position (N, Table 1). A question mark in the table indicates that the ring was not identified in the plate, it swung beyond the plate. There is, however, a defect in this method. It is impossible to record on the plate the exact level of the respiratory phase at which the exposure was made. The method is subjective to the extent that to secure the photograph at the height of the respiratory phases, reliance is placed on the operator.

The measurements taken were those recommended by Moritz<sup>7</sup> and his followers. In the plates the right and left borders were traced, and the outline of the heart's shadow completed by joining arbitrarily the lines representing these. The long and transverse diameters were measured. The angle of inclination of the heart, that is to say, the angle formed by the long diameter and a line drawn to the cardiac apex at right angles with the median line, was recorded. The area of the cardiac outline was measured by the planimeter.

TABLE 2—AVERAGES OF TABLE 1

No of Cases	Weight, Kg	Height, Cm	Age, Yrs	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees
2	53	154	25	13 0	13 5	98	37
2	54	163	30	11 9	13 2	97	43
1	55	158	29	12 8	14 5	122	42
4	56	167	24	12 8	14 2	106	44
4	57	166	23	11 9	14 2	107	50
3	58	167	24	11 8	13 3	100	46
4	59	169	22	12 0	13 7	111	46
9	60	171	24	12 3	13 8	103	41
5	61	168	26	11 9	13 2	101	41
6	62	169	27	12 5	14 1	110	44
11	63	169	28	12 6	13 8	105	43
10	64	170	26	12 7	13 9	106	40
9	65	171	23	12 6	13 9	112	43
6	66	170	23	12 4	14 4	111	45
10	67	170	25	13 7	14 4	110	35
10	68	173	25	13 2	14 5	122	41
12	69	175	28	13 3	14 5	117	41
10	70	175	27	13 1	14 2	108	41
8	71	172	27	13 4	14 8	112	38
9	72	173	23	13 2	14 5	118	43
2	73	175	23	14 3	14 8	114	36
7	74	174	24	13 4	14 4	110	38
8	75	172	25	13 2	14 7	107	39
1	76	176	25	14 5	15 3	121	33
2	77	180	29	12 5	15 4	126	48
2	78	171	26	14 2	14 5	108	31
3	83	180	24	13 5	15 7	123	43
1	86	180	26	13 8	14 7	110	36

In measuring fifty-six pairs of roentgenograms (Tables 3 and 4) it was found that in inspiration and in expiration the transverse diameter was identical in six pairs, greater in inspiration in thirty-one pairs and smaller in nineteen pairs. The long diameters were identical in three pairs, greater in inspiration in forty-two pairs, and smaller in eleven pairs. The area was greater in inspiration in forty-four pairs, smaller in twelve pairs. The angle of inclination was identical in three pairs, greater in inspiration in thirty-nine pairs, and smaller in four-

<sup>7</sup> Moritz, F. Ueber Veränderungen in der Form, grosse und Lage des Herzens beim Uebergang aus horizontalen in vertikale Körperstellung. Zugleich ein zweiter Beitrag zur Methodik der Orthodiagraphie, insbesondere zu der Frage wie die Orthodiagramme auszumessen seien und welche Körperstellung für die Orthodiagraphie des Herzens zu wählen sei, *Deutsch Arch f klin Med* 82 1, 1905.

teen pairs But the difference in size and the difference in position was not great The transverse diameters (less subject to error, as will be pointed out later, than the long diameter, because it does not require the arbitrary location of the apex) differed 5 mm or less in forty-two

TABLE 3—MEASUREMENTS OF THE CARDIAC SHADOW IN INSPIRATION AND EXPIRATION, AND THE DIFFERENCE BETWEEN THE TWO

No	Inspiration				Expiration				Difference Between Inspiration and Expiration			
	Area Sq Cm	Long Diam-eter, Cm	Trans-verse Diam-eter, Cm	Angle, De-grees	Area, Sq Cm	Long Diam-eter, Cm	Trans-verse Diam-eter, Cm	Angle, De-grees	Area, Sq Cm	Long Diam-eter, Cm	Trans-verse Diam-eter, Cm	Angle, De-grees
1	106	141	133	32	116	144	133	35	-10	-03	00	-3
2	101	150	137	33	99	145	144	29	-2	-05	-03	+4
3	88	122	127	33	78	119	125	31	-10	-03	-02	+2
4	92	135	137	29	83	127	128	29	-9	-08	-09	0
5	95	130	130	35	85	125	127	34	-10	+05	-03	-1
6	109	150	144	33	102	146	140	32	-7	-04	-04	+1
7	115	158	147	33	112	149	143	33	+3	-09	-04	0
8	121	153	145	33	103	134	140	27	-18	+19	-05	-6
9	113	141	146	33	117	147	147	33	-4	-06	-01	0
10	100	136	120	40	97	131	125	39	+3	-05	-05	+1
11	110	146	142	37	95	134	127	38	-15	+12	-15	-1
12	90	120	122	36	94	130	124	34	-4	-01	-02	+2
13	114	139	128	34	96	128	116	39	+18	-11	+12	-5
14	108	138	127	35	102	137	126	36	-6	+01	+01	-1
15	109	147	125	40	104	139	132	36	+5	-08	-07	+4
16	95	144	132	37	98	144	136	34	-3	00	-04	+3
17	110	149	145	34	107	149	143	35	-3	00	+02	-1
18	113	145	140	41	104	139	134	35	+9	-06	-06	-6
19	103	137	128	39	100	130	130	38	-3	-02	-02	-1
20	92	134	116	39	96	128	113	40	-4	+06	-03	-1
21	95	133	120	43	93	130	117	39	+2	-03	+03	-4
22	96	135	129	38	98	134	132	35	+12	-01	-03	+3
23	122	162	140	39	108	146	135	34	-14	-16	-05	-5
24	100	132	120	39	103	135	120	35	-3	-03	-09	-4
25	109	145	138	41	104	137	135	34	-5	+08	-03	-7
26	132	148	137	42	112	143	135	36	-20	-05	-02	-6
27	128	148	133	44	124	145	130	45	+4	-03	-03	-6
28	82	135	122	38	85	130	122	39	-3	-05	00	-1
29	119	146	133	40	95	124	128	42	-24	-22	-05	-2
30	122	157	134	41	108	141	134	38	-14	-16	00	-3
31	100	130	125	38	91	136	126	37	+9	-03	-01	-1
32	92	125	105	44	80	123	103	37	-12	-02	-02	+7
33	120	130	130	43	107	135	128	40	-13	-04	-11	-3
34	114	140	128	47	102	130	120	36	-12	-14	-08	-11
35	98	138	124	42	104	144	133	38	-6	-06	-00	+4
36	122	157	140	40	110	158	139	39	-12	-01	-01	+1
37	114	146	130	40	105	140	130	42	-9	-06	00	-2
38	132	150	128	45	115	145	127	41	+17	+05	-01	-4
39	95	138	117	47	90	131	117	41	+5	-07	00	-6
40	124	147	125	44	104	139	136	37	+20	-08	-11	+7
41	140	155	135	49	124	147	130	40	-16	-08	-05	-9
42	124	152	130	45	103	138	124	38	-21	-14	-06	-7
43	86	133	114	40	82	131	119	35	-4	-02	-05	+5
44	109	141	128	46	102	141	122	41	+7	00	-06	-5
45	108	145	123	49	96	136	128	38	+12	+09	-05	-11
46	109	138	128	42	108	140	130	41	-1	-02	-02	-1
47	93	132	123	43	80	126	122	37	-13	-06	-01	-6
48	92	132	122	47	100	135	115	50	-8	-03	-07	-3
49	104	143	122	42	94	140	123	35	-10	-03	-01	-7
50	109	146	125	44	98	131	122	41	+11	-15	-03	-3
51	108	147	125	43	110	140	132	41	-2	-02	-07	-2
52	91	131	105	53	87	125	106	54	-4	-06	-01	-1
53	131	152	132	47	121	144	128	48	-10	-08	-04	-1
54	102	136	125	37	105	138	127	54	-3	-02	-02	-3
55	135	150	148	41	117	141	143	33	-18	-09	-05	-8
56	96	128	123	36	87	127	123	32	-9	-01	00	-4

- indicates that inspiration is greater than expiration

- indicates that inspiration is smaller than expiration

pairs, and 10 cm or less in fifty-two pairs. The long diameters differed 5 mm or less in thirty pairs, and 10 cm or less in forty-eight pairs. The areas differed by 50 sq cm or less in twenty-two pairs, and by 100 sq cm in thirty-seven pairs. Significant differences in size, therefore, do not usually occur during the inspiration and expiration of normal breathing. But the fact that arrests attention is that the heart shadows are larger, that they have longer diameters and that during inspiration the angles increase. There appears no reason to doubt that in certain individuals decrease in these measurements

TABLE 4—DIFFERENCES IN THE MEASUREMENTS TABULATED BETWEEN INSPIRATION AND EXPIRATION

Area		Long Diameter		Transverse Diameter		Angle	
Sq Cm	No of Cases	Cm	No of Cases	Cm	No of Cases	Degrees	Cases
+24	1	+22	1				
+22	1	+21					
+21	1	+20					
+20	2	+19	1				
+19		+18					
+18	3	+17					
+17	1	+16	2				
+16	1	+15	1	+15	1		
+15	1	+14	1	+14			
+14	2	+13		+13			
+13	2	+12	1	+12	1		
+12	4	+11	1	+11	1	+11	2
+11	1	+10	1	+10		+10	
+10	4	+9	3	+9	1	+9	1
+9	5	+8	6	+8	1	+8	1
+8		+7	1	+7	1	+7	4
+7	2	+6	5	+6	3	+6	4
+6	1	+5	6	+5	5	+5	3
+5	3	+4	2	+4	3	+4	7
+4	3	+3	5	+3	6	+3	6
+3	4	+2	2	+2	4	+2	3
+2	2	+1	3	+1	4	+1	8
+1	1	0	3	0	6	0	3
0		-1	2	-1	4	-1	7
-1		-2	4	-2	4	-2	2
-2	2	-3	3	-3	2	-3	2
-3	4	-4		-4	1	-4	
-4	3	-5		-5	3	-5	1
-5		-6	2	-6		-6	1
-6	1	-7		-7	2	-7	1
-7		-8		-8			
-8	1	-9		-9	2		
-9		-10		-10	1		
-10	1						

+ indicates that inspiration is larger than expiration

- indicates that inspiration is smaller than expiration

takes place, but the study of the roentgenograms supplies no explanation for this occurrence. The reason may be sought, perhaps, in peculiarities in the motion of the thorax and of the diaphragm.

The comparison of roentgenograms made in normal inspiration and expiration then, permits the statement that the difference between the two is not great, that, as is expected, the size of the heart shadow is usually greater in inspiration, and that, in this phase, the angle of inclination is usually larger. For clinical purposes, therefore, as will be shown, in a method accompanied by variations so large, the influ-

ence of the phases of normal respiration on the size of the heart may be neglected

The hearts were measured in 208 soldiers. Although the men who were sent were considered by themselves and by the officers who selected them sound and fit for service, forty-seven had, at one time or another, suffered from an acute infectious disease. The infections and the number of men affected were as shown in Table 5. Only the remaining 161 are considered, therefore, in this discussion (Table 1). For the sake of completeness and for the use of others making similar studies the data of the forty-seven other men are given (Tables 6 and 7).

TABLE 5—INFECTIOUS DISEASES REPORTED BY THE REJECTED SOLDIERS

Disease	No of Cases	Other Diseases	No of Cases	Disease	No of Cases	Other Diseases	No of Cases
Typhoid fever	2			Dysentery	2, also	Pneumonia	1
Trench fever	2					Influenza	1
Influenza	11, also	Trench fever	1			Trench fever and gas	1
Gas poisoning	6, also	Dysentery	2	Mumps	5, also	Gas poisoning	1
		Pneumonia	2	Pneumonia	8		
		Rheumatism	1	Scarlet fever	1		

Table 1 gives the following information. The phase of respiration in which each plate was secured, whether plates of both respiratory phases were taken, the weight, height and age, the transverse diameter, the long diameter, and area of the cardiac shadow, and the angle of inclination. Other measurements were not made, they were not considered of special value in this study.

In order to facilitate the study of the data, these are presented in the form of curves. Based on a study of his own<sup>5</sup> and on a collation of published figures, Bardeen<sup>8</sup> has constructed formulae from which he has drawn certain standard curves. In these he has shown that the transverse diameter and the area of the cardiac shadow vary with the weight of the body. For purposes of comparison, these so-called standards are utilized in the following discussion.

The transverse diameter of the heart is considered first. In Bardeen's curve this diameter at 53 kg is 120 cm (Fig 1). From this point, the curve follows practically a straight line. The curve obtained in this study from the average measurements of soldiers, follows this with reasonable closeness. Between 56 and 66 kg and at 74, 75, 77, 83 and 86 kg the averages are below the standard. Elsewhere, they equal or exceed it. The differences are not sufficiently great to justify a conclusion that in respect to this dimension the hearts of the soldiers examined differ materially from the normal. The result of the examinations made by Smith<sup>6</sup> parallel these observations closely. Those

<sup>8</sup> Bardeen, C. R. Tables for Aid in the Determination of the Relative Size of the Heart by Means of the Roentgen Ray, *Am. J. Roentgenol.* 4: 604, 1917.

**TABLE 6—DATA AND MEASUREMENTS OF THE HEARTS OF  
THE SOLDIERS REJECTED**

No	Phase Res- pira- tion	P	Weight, Kg	Height, Cm	Age, Yrs	Trans- verse Diam- eter, Cm	Long Diam- eter, Cm	Area, Sq Cm	Angle, De- grees	Notes
1	I		54	167	25	11 5	12 9	103	50	Typhoid fever
2	I	+	57	172	20	12 0	13 3	95	43	Influenza, trench fever
3	?		58	165	25	13 3	14 7	132	40	Influenza
4	I	+	58	164	25	13 3	14 8	128	44	Gas
5	I		58	161	20	12 4	13 0	96	43	Pneumonia
6	I		58	172	21	11 5	13 6	105	54	Gas
7	I		59	172	24	10 3	13 8	115	59	Influenza
8	I	+	60	167	26	12 4	13 8	98	42	Gas, dysentery
9	I	+	60	163	22	12 8	13 8	109	42	Rheumatism, gas
10	I		61	176	26	12 9	14 2	97	39	Dysentery
11	I		61	168	21	11 2	13 1	88	44	Mumps, gas
12	I		61	173	22	12 3	14 5	128	48	Gas, dysentery
13	I		62	165	25	13 7	15 4	134	40	Mumps
14	I		62	161	29	12 5	14 2	110	42	Gas
15	I	+	63	162	19	12 7	12 2	88	33	Typhoid
16	E		63	171	23	11 5	12 6	91	43	Mumps
17	I		63	174	26	12 0	13 8	118	52	Gas
18	I		63	174	23	11 0	12 7	94	44	Dysentery, pneu- monia
19	I		63	175	24	12 9	15 4	131	55	Gas, pneumonia
20	I	+	64	162	22	13 8	14 5	109	41	Mumps
21	I	+	65	169	30	14 0	14 5	113	41	Mumps—kidneys?
22	I	+	65	171	22	13 7	14 8	132	42	Dysentery, gas, trench fever
23	N	+	66	178	29	12 5	14 7	109	40	Influenza
24	I		66	176	25	12 4	15 7	131	57	Dysentery, influ- enza
25	I	+	67	168	34	13 3	14 1	106	32	Influenza
26	I		67	172	24	11 8	13 6	110	47	Pneumonia
27	I		67	173	23	12 8	15 1	124	47	Dysentery
28	E		67	172	33	13 0	13 9	104	40	Influenza
29	I		67	179	21	12 8	14 7	119	44	Influenza
30	N		68	167	31	13 9	14 4	102	35	Gas, pneumonia
31	I	+	69	165	32	13 0	13 0	95	35	Influenza
32	I	+	69	173	26	13 4	15 7	122	41	Trench fever
33	I		70	173	19	14 7	15 2	125	42	Gas
34	I		70	175	22	14 0	14 6	122	44	Trench fever
35	I		71	173	23	13 8	15 2	103	38	Influenza
36	I		72	178	26	15 5	16 4	136	37	Influenza
37	I		72	169	23	11 8	13 6	115	51	Gas
38	I	+	73	173	23	13 7	15 0	101	33	Scarlet fever
39	I		74	176	22	13 8	14 8	133	34	Influenza
40	I		74	163	31	13 5	14 6	113	33	Influenza
41	I	+	74	176	26	14 0	16 2	122	39	Pneumonia
42	I		75	172	29	14 2	14 3	113	36	Pneumonia
43	I		75	163	28	14 4	15 8	125	52	Pneumonia
44	I ?	+	76	176	26	12 2	12 9	90	36	Pneumonia
45	I		80	183	23	14 3	14 5	103	35	Pneumonia
46	I		82	171	32	13 7	14 5	120	42	Pneumonia
47	N	+	86	176	25	12 8	13 9	114	34	Mumps

Column 2 gives the phase of respiration in which the exposure is made

Column 3 indicates (—) whether exposures were obtained both in inspiration and expiration

Columns 4 to 6 give the weight, height, and age

Columns 7, 8, 9 and 10 give the transverse diameter, the long diameter, the area of the cardiac shadow and the cardiac angle

Column 11 gives notes of interest

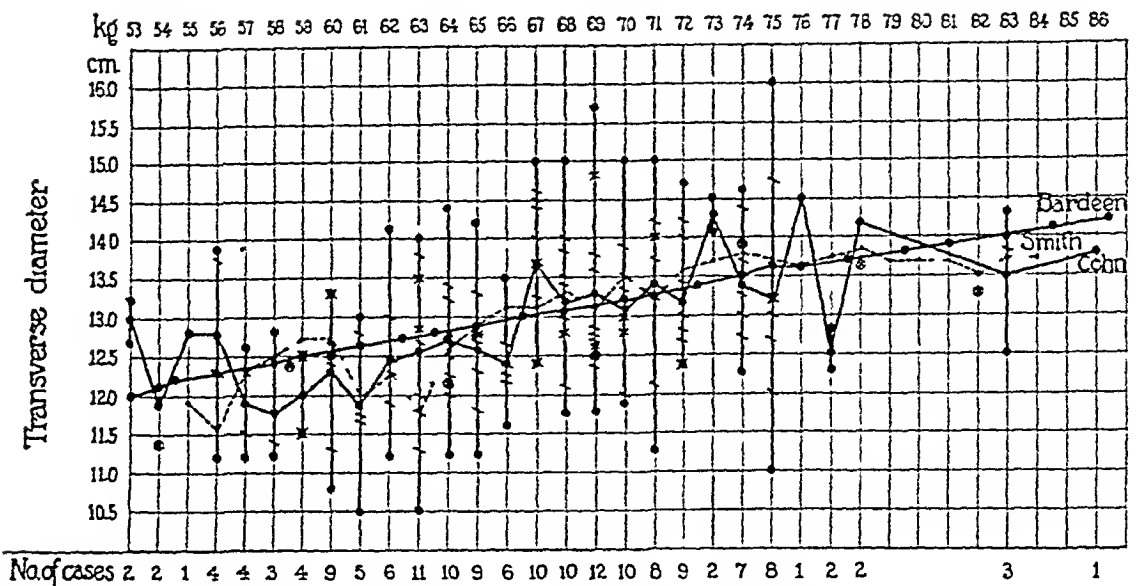


Fig 1—The Transverse Diameter—The ordinates give the diameter, the abscissae the body weight. Below the curves is stated at each weight the number of cases examined at that weight, on which the average is based. The vertical lines represent the range of observations at that weight, the short oblique or horizontal lines which cross these indicate the measurement of each case examined. For comparison the standard curve of Bardeen is given. Smith's curve is likewise shown. X indicates Meakin's and Gunson's average measurement of the hearts of "irritable soldiers."

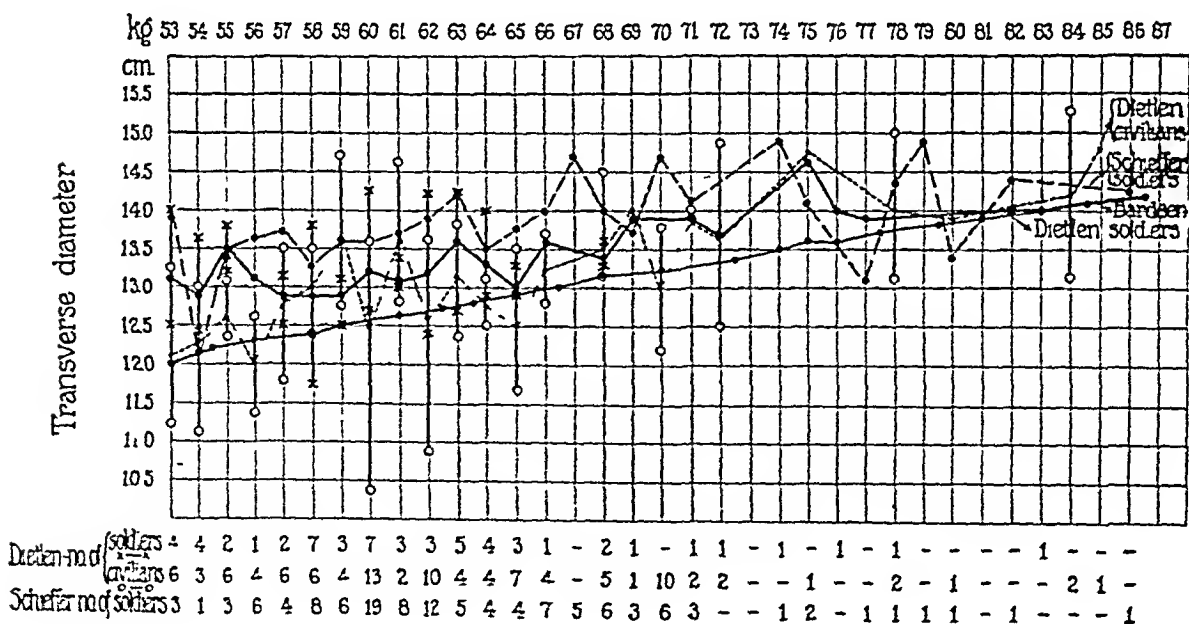


Fig 2—The Transverse Diameter—The ordinates give the diameter, the abscissae the body weight. The dotted line represents Dietlen's civilians. The heavy broken line represents Schieffer's soldiers. For comparison the light unbroken line representing the standard curve of Bardeen is given, and the heavy line represents Dietlen's civilians. The vertical lines at each weight represent the range of Dietlen's observations; x—x, the range for soldiers, o—o, the range for civilians. Below the curve at each weight is stated the number of observations at that weight, on which the average is based.



made by Meakins and Gunson<sup>9</sup> are, on the whole, smaller than the foregoing, but their measurements were taken of the hearts of soldiers who suffered from the "Irritable Heart" Dietlen's<sup>10</sup> figures (Fig 2), on the other hand, both for soldiers and civilians, are a little larger, those for soldiers falling at every weight above the standard, those for civilians falling below it five times—Schieffer's<sup>11</sup> curve (Fig 2), based on the examination of soldiers in Moritz's clinic, is, on the whole, farther still above the standard, once it coincides with it, and twice it falls below it

TABLE 7—AVERAGES OF TABLE 6

No of Cases	Weight, Kg	Height, Cm	Age, Yrs	Transverse Diameter, Cm	Long Diameter, Cm	Area, Sq Cm	Angle, Degrees
1	54	167	25	11.5	12.9	103	50
1	57	172	20	12.0	13.3	95	43
4	58	165	22	12.6	14.0	115	45
1	59	172	24	10.3	13.8	115	59
2	60	165	24	12.6	13.8	103	42
3	61	172	23	12.1	13.9	104	40
2	62	163	27	13.1	14.8	124	41
5	63	171	23	12.0	13.3	104	45
1	64	162	22	13.8	14.5	109	41
2	65	170	26	13.8	14.6	122	41
2	66	177	27	12.4	15.2	120	48
5	67	172	27	12.7	14.2	112	42
1	68	167	31	13.9	14.4	102	35
2	69	169	29	13.2	14.3	103	38
2	70	174	20	14.3	14.9	123	43
1	71	173	23	13.8	15.2	103	38
2	72	173	24	13.6	15.0	125	44
1	73	173	23	13.7	15.0	101	33
3	74	171	26	13.7	15.2	122	35
2	75	167	28	14.3	15.0	119	44
1	76	176	26	12.2	12.9	90	36
1	80	183	23	14.3	14.5	103	35
1	82	171	32	13.7	14.5	120	42
1	86	176	25	12.8	13.9	114	34

Inasmuch as only the transverse diameter may be measured in an objective manner, being alone uninfluenced by the shadows of other viscera, especial importance is attached to this measurement. That divergencies appear in the several curves presented is not of so much interest as that the similarity is significant. Although in each series of examinations (Dietlen, Schieffer, Meakins and Gunson, Smith, Cohn) the number at each weight examined was not great, the curves show that at succeeding weights a gradual, even if not uniform,

9 Meakins, J. C., and Gunson, E. B. Orthodiagraphic Observations on the Size of the Heart in Cases of So-Called "Irritable Heart," Heart 7 1, 1918

10 Dietlen, H. Ueber Grosse und Lage des normalen Herzens und ihre Abhängigkeit von physiologischen Bedingungen, Deutsch Arch f klin Med 88 55, 1906

11 Schieffer. Ueber den Einfluss des Militärdienstes auf die Herzgrosse, Deutsch Arch f klin Med 92 392, 1908

increase in length of this diameter occurs. Since these curves are based on averages, the range of the individual measurements which form the bases of them requires consideration. Bardeen's standard curve, it will be remembered, is constructed from a formula. The widest ranges observed in the present study were 3.5 cm. at 63 kg. (11 cases), 3.8 cm. at 69 kg. (12 cases) and 5.0 cm. at 75 kg. (8 cases). But at 63 kg., 8 of 11 cases fell within 2.0 cm., at 69 kg., 7 of 12 cases fell within 1.2 cm., at 75 kg., 5 of 8 cases fell within 1.2 cm. The ranges which are usual are, therefore, not wide. In Dietlen's fifty-nine soldiers these were, for example, at 53 kg., 1.5 cm.; at 54 kg., 1.2 cm.; at 58 kg., 2.1 cm.; at 60 kg., 1.6 cm.; at 62 kg., 1.8 cm.; at 63 kg., 1.5 cm.; at 65 kg., 0.4 cm. If the civilians are included they were at 53 kg., 2.8 cm.; at 54 kg., 2.5 cm.; at 58 kg., 2.1 cm.; at 60 kg., 3.9 cm.; at 62 kg., 3.3 cm.; at 63 kg., 1.8 cm.; at 65 kg., 1.8 cm.

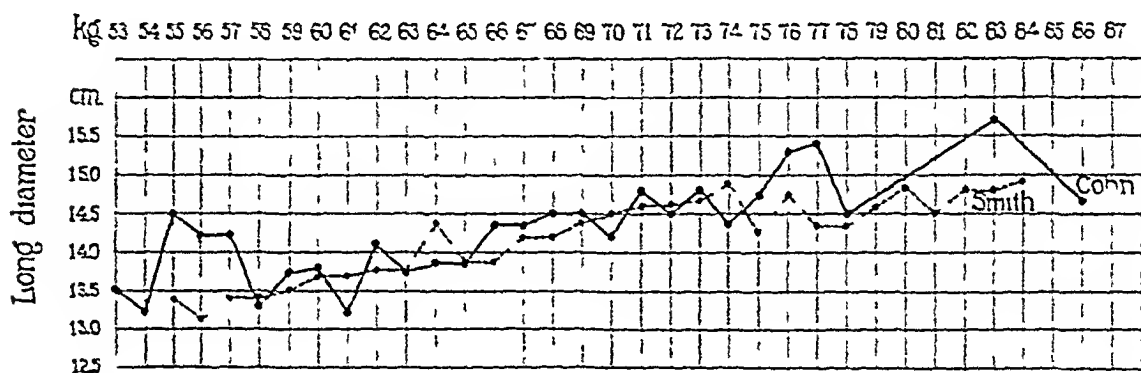


Fig 3—The Long Diameter—The ordinates give the diameter, the abscissae the body weight. The unbroken line represents the curve of the present observations. Those of Smith are given for comparison. The number of men examined at each weight is the same as in Curve 1.

The curve of the average long diameter is compared with the curve obtained by Smith (Fig 3). The two approximate each other closely. The difficulty of locating the apex precisely in the photographic plate makes the estimation of the long diameter inexact. The same difficulty is experienced in outlining and measuring the area of the heart's shadow. It is, therefore, considered under that head.

To delimit the area of the cardiac shadow requires that the extremities of the lines representing the right and left borders of the heart be joined by curved lines drawn arbitrarily. With experience these lines are probably drawn by different observers in a consistent manner, but no doubt each observer draws them differently. The outline, as Bardeen<sup>5</sup> points out, 'will include within the territory of the heart the right and left atria and the cardiac extremity of the pulmonary artery and of the aorta. A small portion of the left auricle may be cut off by the line that curves toward the right from the left border, but as a rule this is insignificant.' The outline is, therefore, as Bardeen says,

a modified outline of the heart. But the completed outline fails in exact representation also because of the difficulty, indeed, often because of the impossibility, of locating the apex in certain individuals. On being able to locate this point accurately depends the value of the measurement, both of the long diameter and of the area. Although the subject of heart disease is not considered in this paper, it may be pointed out that this difficulty is increased further in cases of heart failure, because the maneuver of exposing by deep breathing a length of the left border of the heart shadow sufficiently great to insure accuracy is often extremely difficult. Mention is made here of heart failure because a technic for the study of the size of the heart in this condition and in the stages which lead to it is a matter of concern in the clinic, where criteria for judging of size are earnestly wanted. For this reason, and in order to avoid the exaggeration in size due to deep breathing, the method of breathing while securing the roentgenograms was modified. In addition to the difficulty of locating the apex, the method of completing the outline from the apex to the right border also varies, as has been said, with individual observers. In this study, for instance, the lower outline was drawn in a conservative manner so that the cardiac area was less by several square centimeters than that which might have been obtained. Making exposures during normal breathing tended to increase this reduction, as the studies on the effect of deep breathing show. But, as has been pointed out, photographing in deep inspiration occasions an error in the other direction, it permits an increase in the volume of blood in the heart, and, consequently, in the area of its shadow, especially in the initial phase when the breath is held. Caution in respect to two other points should be expressed in considering the significance of this outline for clinical purposes. First, the line beginning at the junction of the right border with the diaphragm follows along the right border and passes beyond to the point where it joins the upper extremity of the left border, including within the outline most of the auricles and portions of the great vessels. This line does not follow or represent the ventricles. Second, the line joining the lower ends of the two borders, about the precise drawing of which, as has been said, there is the greater difficulty, is concerned with outlining the margin of one ventricle—the right ventricle. Of the entire cardiac shadow, therefore, only the line of the left border, and indeed, only a portion of this line, accurately follows a ventricular structure. It is, of course, appreciated that what has been said of the line of the right border applies to the value of the transverse diameter as well as to that of the area of the completed outline. No attempt is made at this time to estimate the precise importance of these points, they are matters which require consideration in the study of the abnormal heart.

Although the results depend on these variable factors the curves (Fig 4) based on the averaged observations of the area of the heart's shadow show surprising similarities. The standard curve constructed according to Bardeen's formula is shown for comparison. The lowermost curve represents the averages of the observations obtained in this study. Except for the single observation at 55 kg the curve lies below the standard. This position is expected in part because the measurements were made from plates taken in the standing position. Curves based on the measurement of shadows obtained as was the standard curve in the sitting position have higher values. Bardeen estimates the reduction in size resulting from changing from the prone

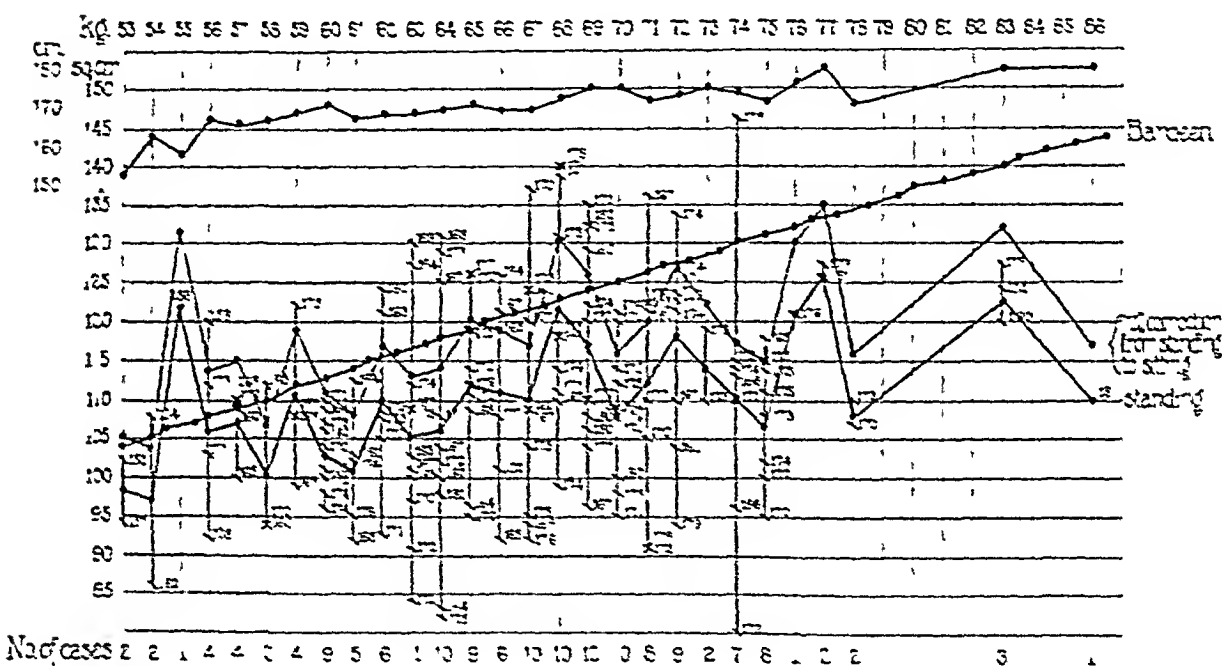


Fig 4—The Area of the Cardiac Shadow—The ordinates give the area in sq cm the abscissae the body weight. Below the curves is stated at each weight the number of men examined at that weight on which the average is based. The vertical lines represent the range of observations at that weight; the short oblique lines which cross these indicate the measurement of each case examined. Opposite the short lines is placed the height of that individual. The lowest curve represents the average measurements actually observed in the standing position. The curve above and parallel with this is a corrected curve giving the estimated area in the sitting position, 73 per cent. being added to the lower curve. For comparison the standard curve of Bardeen (the third curve from below upward) is given. The uppermost curve gives the average height of the men examined.

to the sitting position to be from 5 to 7 per cent, and the reduction from the prone to the standing position 13.3 per cent. From the sitting to the standing position a reduction therefore, of 7.3 per cent. is expected. A correction of 7.3 per cent. was therefore made. The curve so corrected approximates the standard curve. The corrected

curve then exceeds the standard curve eleven times (53, 55, 56, 57, 59, 62, 65, 68, 69, 72, 77 kg), it falls below it seventeen times (54, 58, 60, 61, 63, 64, 66, 67, 70, 71, 73, 74, 75, 76, 78, 83, 86 kg)

It is important also to consider the range of observation at each weight from which the average curves are constructed, especially in applying data to the problem of the individual case. In the present study (Fig 4 and Table 8) the greatest range is 64 sq cm at 74 kg (seven cases), the smallest is 20 sq cm at 77 kg (two cases). At

TABLE 8—BODY WEIGHT ACCORDING TO RANGE OF CARDIAC AREA

Range, Sq Cm	Weight in Kg			Range, Sq Cm	Weight in Kg		
	Cohn	Schleffer	Dietlen		Cohn	Schleffer	Dietlen
66	74	—	—	24	59	61	63
62	—	63	—	23	75	—	—
49	64	—	—	22	54	63	—
46	63	—	—	21	61	—	—
45	67, 71	—	—	20	—	55	64, 70
42	—	60	—	19	—	—	53, 55, 78
41	68	—	—	18	58	64, 71	56
40	72	—	—	17	—	75	66
39	69	—	—	16	—	—	54, 72
38	—	69	—	15	—	57	—
36	—	—	52	14	60	—	—
34	66	62, 56	—	11	—	59	59
33	—	65, 66	—	10	57	—	—
32	—	68	—	9	73	—	—
31	62, 65	—	—	8	53	—	—
29	—	—	60, 62	7	83	—	84
28	56	70	58	5	—	52	—
27	—	—	57, 61, 68	3	78	—	71
26	70	58	65	2	77	—	—
25	—	67	—				

TABLE 9—RANGE OF CARDIAC AREA OF THE GREATER NUMBER OF CASES AT WEIGHTS WHERE THE GREATEST RANGES OCCURRED

Range, Sq Cm	Weight, Kg	Range of Greater Number of Cases
66	74	4 of the 7 cases within 5 sq cm
49	64	5 of the 10 cases within 10 sq cm
45	71	5 of the 8 cases within 17 sq cm
45	67	6 of the 10 cases within 20 sq cm
46	63	7 of the 11 cases within 15 sq cm
41	68	5 of the 10 cases within 8 sq cm
40	72	6 of the 9 cases within 12 sq cm
40	69	7 of the 12 cases within 18 sq cm
34	66	Scattered through entire range
31	65	5 of the 9 cases within 10 sq cm
31	62	3 of the 6 cases within 4 sq cm
28	56	2 of the 4 cases within 9 sq cm

eight weights (53, 57, 58, 60, 73, 77, 78, 83 kg) the range is less than 20 sq cm, it is between 21 and 30 sq cm in six instances (54, 56, 59, 61, 70, 75 kg), between 31 and 40 sq cm in five instances (62, 65, 66, 69, 72 kg), between 41 and 50 sq cm in five instances (63, 64, 67, 68, 71 kg), and once it is 66 sq cm (74 kg). But where the range is greatest, as at 74 kg, four of the seven cases actually lie within 5 sq cm (Table 9). At other weights, likewise where the range is wide, the occasional case rather than the greater number, is responsible

for the wide limits. The range does not appear to be influenced by the weight (Table 10). For comparison the data of Dietlen and Schieffer are added.

A comparison of this result with the results obtained by others is instructive. The data published by Dietlen<sup>10</sup> Schieffer,<sup>11</sup> Bardeen,<sup>8</sup> and Smith<sup>6</sup> have, therefore, been arranged in curves in the same way. Dietlen's data include measurements of both soldiers and of male civilians. Separate curves for these two classes have been made. Arranged in this manner (Fig 5), Bardeen's curve being included for comparison, the curve for soldiers coincides with the standard twice (54, 67), it lies above it thirteen times (52, 53, 56, 58, 59, 61, 63, 66,

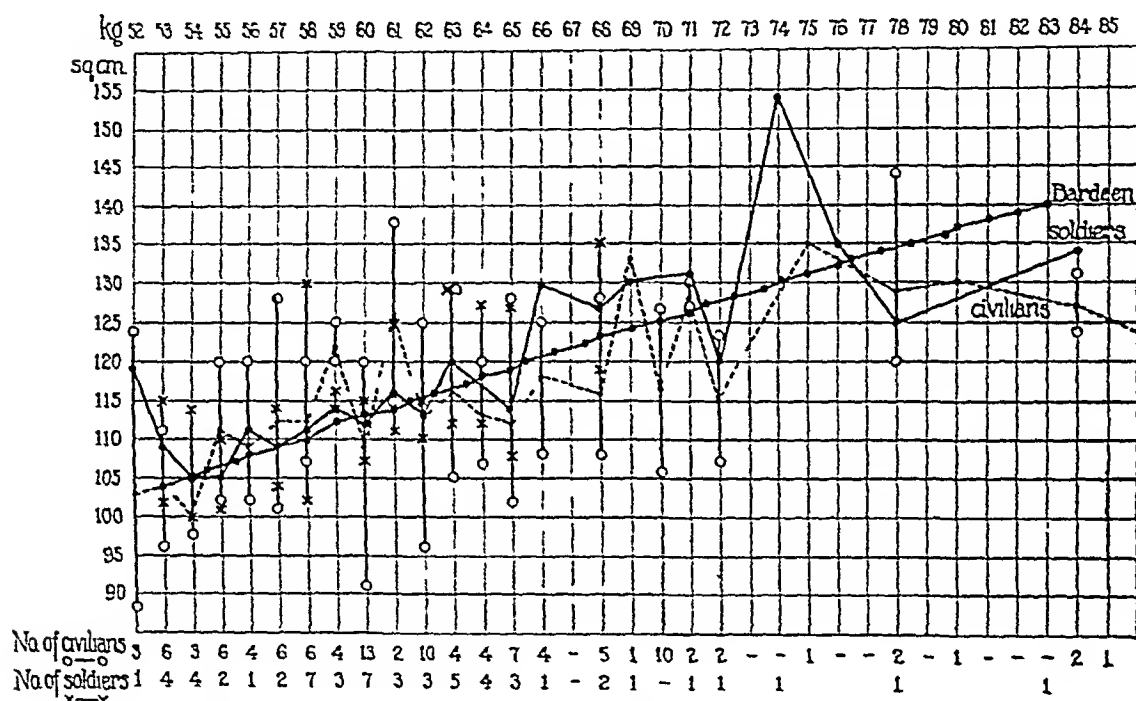


Fig 5—The Area of the Cardiac Shadow Based on Dietlen's Tables—Ordinates and abscissae as in Curve 4. Below the curve is stated at each weight the number of soldiers and of civilian males examined at that weight, on which the average is based. The vertical lines represent the range of observations at each weight. o—o represents the range for civilians. x—x represents the range for soldiers. The standard curve of Bardeen is given for comparison.

68, 69, 71, 74, 76 kg), and below it eight times (55, 60, 62, 65, 72, 78, 83 kg). On the whole, therefore, it lies above rather than below. The curve for male civilians coincides with the standard twice (53, 63 kg), it lies above it nine times (55, 56, 57, 58, 59, 61, 69, 71, 75 kg), and below it thirteen times (54, 60, 62, 64, 65, 66, 68, 70, 72, 78, 80, 84, 85 kg). This curve on the whole then, lies below it. The soldiers' curve accordingly represents slightly larger hearts than that for civilians. And it exceeds the curve resulting from the present

study With three exceptions Schieffer's curve (Fig 6) lies uniformly above the standard and represents hearts larger than those in Dietlen's curve Smith's curve (Fig 7) follows the standard closely It coincides with it seven times, falls below it twenty-two times and exceeds it once

Interesting as is the comparison of the present curve with Bardeen's standard and the other curves, of greater importance is a consideration of the range The ranges found by Dietlen extend from 3 to 36 sq cm (Fig 5 and Table 8), and those found by Schieffer from 5 to 62 sq cm (Fig 6 and Table 8) The widest range given by Smith is 11.0 sq cm (Fig 7) It would be interesting to know the range of

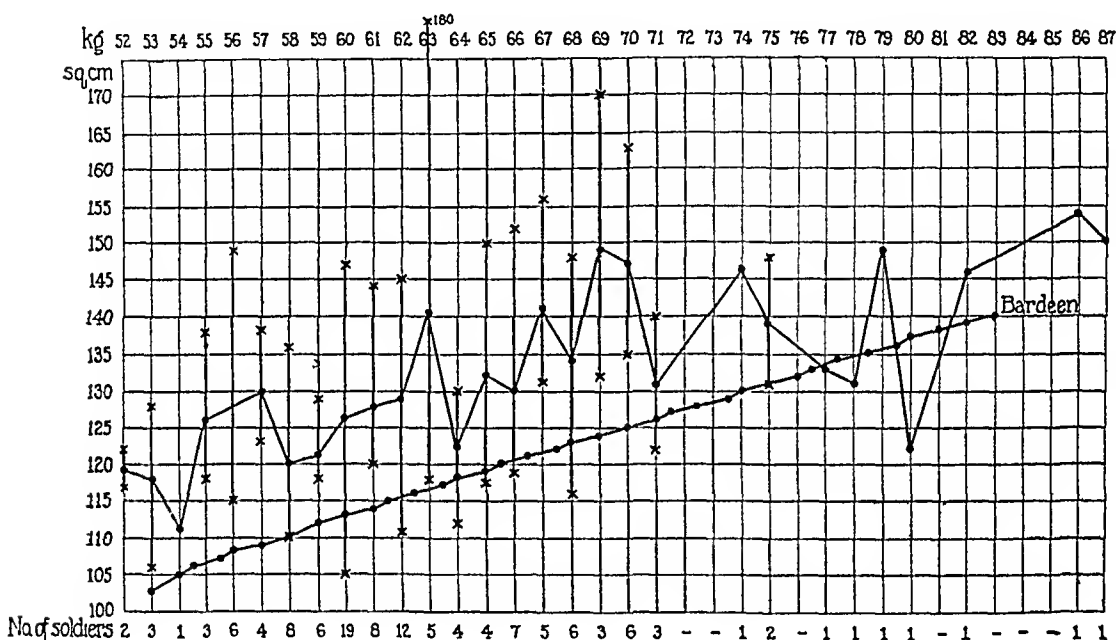


Fig 6—The Area of the Cardiac Shadow Based on Schieffer's Table—Ordinates and abscissae as in Curve 4 Below the curve is stated at each weight the number of soldiers examined at that weight, on which the average is based The vertical lines represent the range of observations at each weight The standard curve of Bardeen is given for comparison

observed areas at each weight in Bardeen's cases, but this information is not given in his papers He gives, however, the average percentage of divergence from the standard curves for each 10 kg of body weight for athletes Between 51 and 60 kg the deviation of the average area was 4.6 per cent. (B, Fig 8) below the standard, between 61 and 70 kg it was 4.4 per cent above, between 71 and 80 kg it was 2.7 per cent above, and between 81 and 90 kg it was 2.9 per cent below For comparison the deviations from the standard found in the study now presented are arranged in the same manner (C, Fig 8) The percentage is based on the curve corrected for position of the body For corre-

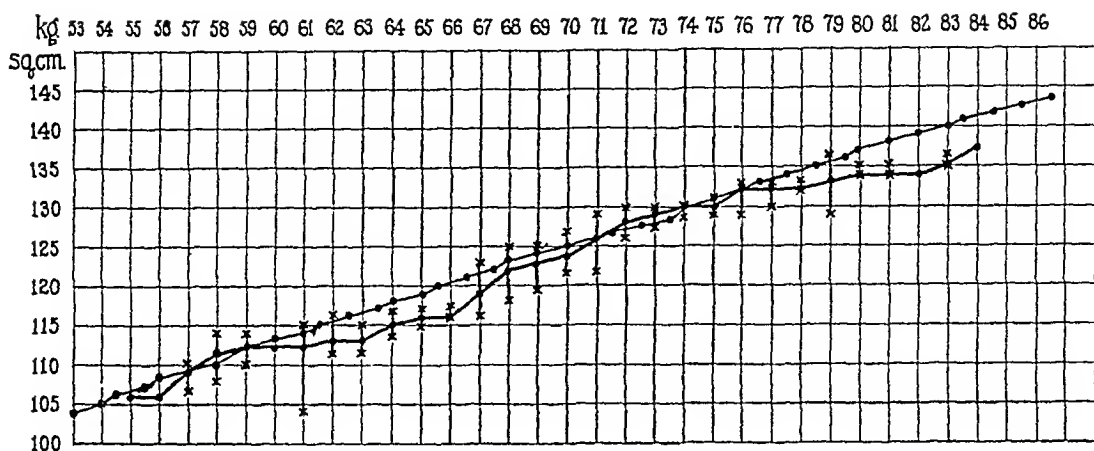


Fig 7—The Area of the Cardiac Shadow Based on Smith's Curve and Tables—Ordinates and abscissae as in Curve 4 The vertical lines represent the range of measurements at each weight The standard curve of Bardeen is given for comparison

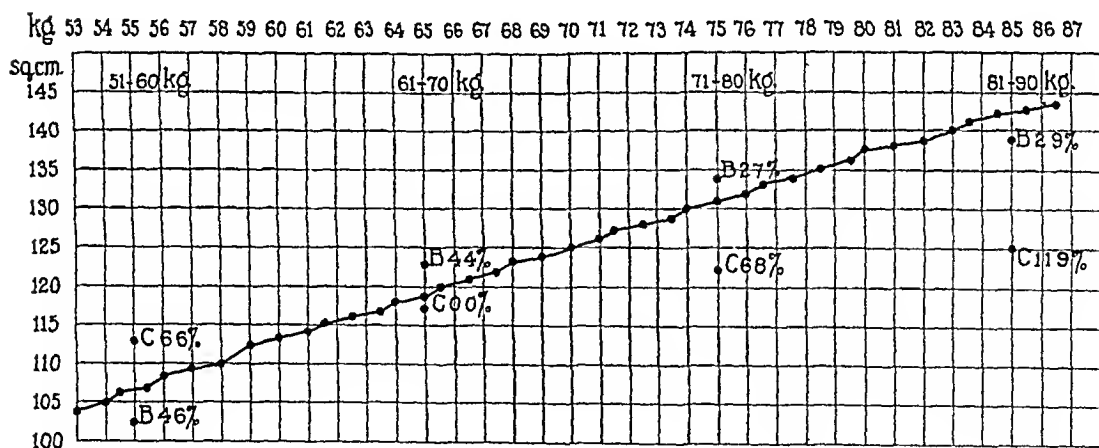


Fig 8—The standard curve of Bardeen is given The average areas of the men examined at weights between 51 and 60, 61 and 70, 71 and 80, 81 and 90 have been inserted for the series now presented (C) and for the figures published by Bardeen (B) Opposite each is given the percentage deviation from the standard curve



sponding weights they are 66 per cent above, coincident with the standard, 68 per cent below, and 138 per cent below

TABLE 10—RANGE OF CARDIAC AREA ACCORDING TO BODY WEIGHT

Weight, Kg	Range		
	Cohn	Scheffer	Dietlen
52		5 sq cm	36 sq cm
53	8 sq cm	22	19
54	22 sq cm	1 case	16
55	1 case	20 sq cm	19
56	28 sq cm	34	18
57	10	15	27
58	18	26	28
59	24	11	11
60	14	42	29
61	21	24	27
62	31	34	29
63	46	62	24
64	49	18	20
65	31	33	26
66	34	33	17
67	45	25	
68	41	32	27
69	39	38	1 case
70	26	28	20 sq cm
71	45	18	3
72	40		16
73	9		
74	66	1 case	1 case
75	23	17 sq cm	1 case
76	1 case		1 case
77	2 sq cm	1 case	
78	3	1 case	19 sq cm
79		1 case	
80		1 case	1 case
81			
82		1 case	
83	7		1 case
84			7 sq cm
85			1 case
86	1 case	1 case	
87		1 case	

The curves, then, all show a progressive, even if irregular, increase in the area of the heart's shadow. The usefulness of so-called standard curves, constructed from observed averages, depends, however, on the closeness with which the measurements of the individuals observed, approximate to these curves. Here there is a difficulty, for the wide range of the measurements reduces the value of the average figures. This difficulty apparently does not depend on the technic nor on the individual observer, for it appears in the curves of each.

It has been shown by Dietlen and others that the heart increases in size with the body height. This result is expected because of the usual relation of height to weight. In general therefore, the curves plotted for weight and for height should be similar. The heights of these 161 soldiers have been averaged and plotted at each kilogram of weight (Fig 4). At 53 kg the height is 153 cm. From here the curve ascends not quite in a regular fashion to 83 kg where the height is 180 cm. The height of each individual examined has also been introduced in the curve (Fig 4) on the vertical lines representing range,

opposite the point indicating the area of the cardiac shadow of each individual. The heights at each weight as the curve shows vary through an extended range (Table 11). Under these circumstances, the suggestion quoted by Schieffler that the area is numerically equal to the height less 50, is scarcely tenable.

TABLE 11—RANGE OF HEIGHT AT VARIOUS BODY WEIGHTS

Height, Cm	Weight, Kg	Height, Cm	Weight, Kg	Height, Cm	Weight, Kg
21	60	11	70, 72	9	59
20	74	13	65	7	58
18	66	12	57	5	53, 73
17	61	11	63, 68, 71	3	73, 83
15	56, 61, 67, 69	10	62, 75	2	51, 77

Finally, the relation of the angle of cardiac inclination to other measurements has been studied, but there appears to be no rule relating this to the weight, height, or to any other measurement. The introduction of the use of the angle to express what is now indicated by the phrases "transversely lying heart" or "vertically hanging heart" or "pendulous heart" may, however, simplify reference to this phase of physical examination.

#### SUMMARY AND DISCUSSION

The attempt was made in this study to learn the size, in comparison with that of civilians, of the hearts of soldiers who had undergone the exertion of actual warfare. The data of soldiers available for comparison are those of Dietlen, Schieffler and Meakins and Gunson, and for civilians those of Dietlen. Dietlen's curve for area in general resembles Bardeen's standard, Schieffler's exceeds it, the one now presented is a little below it. The differences among the three are probably due to differences in technique of the observers. For transverse diameters, Dietlen's curve lies above Bardeen's standard, the present one lies below it. Schieffler's curve is higher than Dietlen's. If allowance were made (13 per cent) for the differences between the lying and the standing position, the present curve would exceed Dietlen's and equal Schieffler's. The curves for area and transverse diameters given by Dietlen for civilians differ slightly, but not materially, from those of soldiers. The curves, therefore, do not indicate that soldiers exposed as were these, exhibit larger hearts than normal individuals. Against this conclusion must be set the post-mortem figures given by Karsner<sup>12</sup> for the hearts of British soldiers who were 27 years of age, and who had served twenty-two months. These were

<sup>12</sup> Karsner, H. T. Acute Endocarditis Following War Wounds, Including Notes of Heart Weight and Arteriosclerosis in Soldiers, Arch Int Med 22: 296, 1918.

larger than the controls. If the requirements set by Karsner are sound, enlargement may not be expected in our soldiers whose average age was 24 and whose length of service was usually less than twenty-two months. Furthermore, the examinations here reported were conducted in May, 1919, six months after the cessation of hostilities. Although within that period many had undergone severe exertion, the amount of work they performed probably decreased. A diminution in size of the heart from the maximum reached in November, 1918, may have taken place, but no data are available to indicate whether decreasing the amount of work affects the subsequent size of the heart.

The technic differed from that usually employed in that the plates were taken for the most part during normal inspiration. There is a twofold reason for this, first, it avoids the increase of the heart's size which occurs during deep inspiration. A more nearly normal heart is photographed. Second, it is more likely to provide a standard against which the pathologic heart may be measured. For, as has been pointed out, in increasing heart failure, it becomes progressively more difficult to utilize the method which obliges the subject to breathe deeply and to hold the breath. The technic here employed does not require holding the breath and avoids the artificially large heart. There would probably be no objection to this alteration in technic were it not that exposures made in deep breathing lighten the lung fields, so permitting a sharper image of the heart, and expose in certain individuals, especially those in whom the angle of inclination of the heart is small, a greater extent of the heart's outlines. In the last point there is force. It is not, however, so cogent a reason as it appears to be, for deep breathing aids in locating the apex of the heart and in drawing the long diameter and the area. But these measurements are not superior in value to the transverse diameter, for this diameter increases with the body weight as do the others, it shows no greater variation at each weight, and it can be taken accurately without reference to respiration, and in any case involves no uncertainty such as is necessary in locating the apex and drawing the line indicating the border of the right ventricle.

The value for the present of so-called standard and average curves of cardiac measurements for use in the clinic is questioned. For this reason the range of the measurements for given weights has been emphasized. The difficulty in the use of these curves is illustrated in comparing the cardiac area of a soldier weighing 54 kg with that of one weighing 86 kg. The areas of the two (Curve 4) are 108 sq cm and 110, respectively. And, again, in comparing the cardiac area of a soldier weighing 56 kg with one weighing 83 kg, the areas of both being 120 sq cm. Similar comparisons can be made in Dietlen's and Schieffer's curves (Figs 5 and 6). For the clinic curves of this nature

do not solve the problem of supplying adequate criteria for judging the normality of a given heart. There is, still, necessity for more than a single criterion, such as size. In other connections these curves have a signal usefulness, they may, indeed, serve as bases for studies, in which, combined with other factors, satisfactory criteria for clinical use will be evolved.

#### CONCLUSIONS

1 In normal breathing the difference in the size of the heart during inspiration and expiration may be neglected.

2 The use of the transverse diameter of the heart shadow is a satisfactory measurement. It is as useful as and less uncertain than the long diameter or the area.

3 The range of the observed measurements interferes with the usefulness for the clinic of standard and average curves.

4 The hearts of soldiers examined under conditions stated are not larger than those of normal individuals.

# TELEROENTGEN MEASUREMENTS OF THE HEARTS OF NORMAL SOLDIERS \*

BERTNARD SMITH, M D

LOS ANGELES

Teleroentgen measurements were made on 277 men selected from the orthopedic service for the purpose of securing statistics on the heart size of soldiers who had had active fighting service overseas. Only those men were selected for this study who had been free from cardiac symptoms during their period of military service and who had had no infectious disease since entering the army. Each man whose measurements are reported had completed his training without difficulty, had taken full part in forced marches overseas and had had at least three months of active fighting. Most of the measurements were taken immediately before the men were discharged from the hospital and all the patients were well advanced in convalescence.

The same technic was followed throughout the series. All plates were from one to four seconds' duration, depending on the thickness from the plate. The upright of the tube stand was ruled in inches to correspond to the scale on the screen stand, and with plumbline markings for the lateral position of the tube, the adjustment to a position opposite the center of the plate could be made easily and quickly. When in position, facing the plate, the subject took a deep breath and then exhaled as completely as possible. After this he took a "half breath" on command and this was held for the exposure. Exposures were from one to four seconds' duration, depending on the thickness of the chest wall.

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\* Report of studies made on the Cardiovascular Service, U S Army General Hospital No 9, Lakewood, N J

NOTE—The influence of work, such as military campaigning or training for athletic competition, on the size of the heart is still not satisfactorily known. It seemed unwise, therefore, to neglect the opportunity to study exactly the size of the hearts of soldiers after the campaign in France. To be most serviceable, the study should have been made in France in November, 1918. Unfortunately, proper facilities for doing the work were not available. Although less satisfactory, it was decided that information of sufficient usefulness could still be obtained after the return of troops to the United States. A number of soldiers were, therefore, examined simultaneously at U S General Hospital No 9, at Lakewood, N J and at the Rockefeller Institute. The results of these studies are given in these papers by B. Smith and A. E. Cohn.

From the roentgenograms obtained in this way the following measurements were made

- 1 MI Distance from the midline to the most distant left border
- 2 Mr Distance from the midline to the most distant right border
- 3 TD The sum of MI and Mr has been taken for the value of the transverse diameter
- 4 LD The maximum long diameter, measured from the right auricular notch to the most distant apical border
- 5 BD The maximum broad diameter measured at right angles from the long diameter to the most distant borders above and below
- 6 The angle formed by the transverse and long diameters
- 7 Diameter of the aortic arch
- 8 The parallel ray silhouette area,<sup>1</sup> estimated with the planimeter From this area the volume was calculated by Bardeen's formula<sup>2</sup>

In Table 1 the figures for transverse diameters, long diameter and areas are compared with the Dietlen<sup>3</sup> and Bardeen<sup>4</sup> tables for normals Dietlen's figures were obtained by the orthodiagraphic method, with the subjects recumbent, and the Bardeen measurements were made with the subjects in the sitting position Bardeen states that the transverse diameter is about 7 per cent less for the standing than for the recumbent position This possible variation with a difference of position has not been considered in the tables of this report, but the figures given are the measurements as made from the plates The Bardeen figures in Table 1 are the approximate values for the ranges of weight

TABLE 1—COMPARISON OF DIAMETERS AND AREA WITH THE DIETLEN AND BARDEEN NORMALS

Weight Kg	Soldiers				Dietlen Table				Bardeen Table	
	Cases	T D, Cm	L D, Cm	Area, Cm	Cases	T D, Cm	L D, Cm	Area, Sq Cm	T D, Cm	Area, Sq Cm
55-59	40	12.5	13.6	111	39	12.9	14.0	112	12.4	110
60-64	82	12.1	13.9	113	54	13.1	14.1	114	12.7	116
65-69	61	13.1	14.1	118	24	13.2	14.5	118	13.0	121
70-74	50	13.5	14.6	127	18	13.4	14.8	122	13.4	128
75-79	35	13.7	14.5	131	5	14.3	15.5	131	13.7	124
80-84	9	13.7	14.7	135	5	14.4	15.3	133	14.0	140

The figures for diameter and area from the soldiers are all well within the normal range If the measurements are averaged for the ranges in body weight, and the comparison to the normal tables is expressed in percentages, the variation is very slight In Table 2 the measurements from the 277 soldiers are given as percentages of the Dietlen and Bardeen figures It should be remembered, that the soldiers had been in hospitals for several months convalescing from leg and arm wounds, and during this period of inactivity many had

1 Bardeen, C R Am J Roentgenol 4 604, 1917

2 Bardeen, C R Am J Anat 23 423 1918

3 Dietlen H Deutsch Arch f klin Med 88 55 1907

4 U S Army X-Ray Manual, p 414

gained in weight to a figure above their normal. This gain was due more to an increase of fat than of skeletal muscle. In the table of individual measurements (Table 8) it is seen that the measurements show a greater variation from the normal (below normal) in those men with the higher weight.

TABLE 2—PERCENTAGE RELATION OF MEASUREMENTS OF SOLDIERS WHEN COMPARED WITH THE DIETLEN AND BARDEEN NORMALS

Weight, Kg	Dietlen Normals			Bardeen Normals	
	T D, %	L D, %	Area, %	T D, %	Area, %
55-59	95	95	97	93	99
60-64	94	96	99	97	98
65-69	99	98	99	100	98
70-74	100	99	100	100	100
75-79	95	94	100	100	99
80-84	95	96	100	99	97

The heart measurements from the soldiers differ but very little from the normals when compared by weight. For the total series the transverse diameters average about 5 per cent less than the Dietlen measurements, and 1 per cent less than the normals of Bardeen. The long and broad diameters have a general average of 4 per cent less than those of the Dietlen table. When the areas are compared it is found that the average with the soldiers' hearts is 1 per cent less than Dietlen's normals and 15 per cent below the figures given by Bardeen.

Dietlen<sup>3</sup> has compared his normal measurements by height, and in Table 3 the figures for this series are grouped for the same height ranges. The measurements for area and for the three diameters come within 3 per cent of the Dietlen normal figures.

TABLE 3—MEASUREMENTS COMPARED BY HEIGHT WITH DIETLEN'S NORMALS

Height	Soldiers						Dietlen's Normals					
	Cases	MI, Cm	Mr, Cm	L D, Cm	B D, Cm	Area Sq Cm	Cases	MI, Cm	Mr, Cm	L D, Cm	B D, Cm	Area Sq Cm
155-164	18	4.0	8.3	13.3	9.9	111	72	4.1	8.7	13.8	9.9	109
165-174	174	4.1	8.5	13.1	10.2	118	77	4.2	8.8	14.1	10.3	116
175-187	185	4.3	8.7	14.2	10.7	122	29	4.4	9.1	14.8	10.7	127

Measurements of the transverse diameter may have a wide range even with the same body weight. In the twenty-two cases with a body weight of 59 kilograms (Table 4), the transverse diameters range from 11.5 cm to 14.0 cm. Also, a heart with a transverse diameter of 12.7 cm may have a slightly larger area than the heart with a diameter of 14.0 cm. If other diameters are measured, this variation in the transverse figures is found to be due to the general heart shape. There is danger of serious error if an opinion of heart size is based on a measurement of the transverse diameter alone, especially in individual

cases, without attention having been given to the general form and position of the heart. The angle formed by the transverse and long diameter can often be of value in deciding the question of size in doubtful cases, especially when the area has not been determined.

TABLE 4—MEASUREMENTS OF THE TRANSVERSE, LONG AND BROAD DIAMETERS, WITH AREA AND CARDIAC ANGLE, GROUPED BY WEIGHT

Weight, Kg	Cases	Height Cm	Age	T D, Cm	L D, Cm	B D, Cm	Area Sq Cm	Aortic Arch, Cm	Angle Degree
55	2	170	24	11.9	13.4	10.0	106	4.7	50
56	1	165	23	11.6	13.1	9.6	106	4.4	55
57	4	167	24	12.3	13.4	9.8	108	4.5	42
58	11	168	24	12.5	13.4	9.8	111	4.6	42
59	22	170	26	12.7	13.5	9.8	112	4.6	44
60	1	175	23	12.7	13.7	10.1	112	4.7	49
61	26	172	24	12.0	13.7	10.4	112	4.6	47
62	12	171	25	12.3	13.8	10.1	113	4.5	42
63	26	172	25	11.8	13.8	10.3	113	4.5	42
64	17	175	24	12.6	14.4	10.6	115	4.6	43
65	14	175	25	12.9	13.9	10.7	116	4.7	43
66	4	176	25	13.1	13.9	10.5	116	4.5	48
67	14	174	26	13.1	14.2	10.6	119	4.6	41
68	19	175	25	13.3	14.2	10.6	122	4.6	45
69	10	174	25	13.1	14.4	10.5	123	4.6	39
70	15	175	26	13.5	14.5	10.6	124	4.7	44
71	14	175	27	13.3	14.6	10.6	126	4.7	46
72	10	177	26	13.6	14.6	10.5	128	4.6	39
73	5	175	28	13.7	14.7	10.3	129	4.9	38
74	6	180	27	13.8	14.9	10.3	130	4.7	42
75	13	177	28	13.7	14.3	10.6	130	4.7	40
76	8	178	26	13.6	14.7	10.8	132	4.7	44
77	8	174	26	13.7	14.4	10.7	132	4.7	37
78	2	176	26	13.8	14.4	10.4	132	4.6	42
79	4	179	24	13.7	14.7	10.8	133	4.6	42
80	2	179	28	13.7	14.9	11.2	134	4.8	48
81	3	174	28	13.7	14.5	10.8	134	4.7	37
82	1	173	25	13.5	14.8	10.7	134	4.5	41
83	2	178	27	13.7	14.8	10.9	135	4.7	34
84	1	185	38	13.7	14.9	11.4	137	4.5	46

TABLE 5—DIAMETERS, AREA AND ANGLE COMPARED BY HEIGHTS

Height, Kg	Cases	T D, Cm	L D, Cm	B D, Cm	Area, Sq Cm	Angle, Degree
155	2	12.0	13.5	10.1	111	50
157	2	13.1	12.8	9.6	111	35
160	6	12.7	13.3	10.1	112	43
163	8	12.2	13.4	9.9	111	42
165	11	12.7	13.5	10.1	116	40
168	30	12.9	14.0	10.3	118	38
170	28	12.9	14.1	10.4	120	41
173	44	13.3	14.1	10.2	119	42
175	36	12.6	14.2	10.2	119	46
178	62	13.0	14.1	10.2	122	44
180	32	13.3	14.4	10.6	127	43
183	8	13.5	14.6	10.5	127	42
185	8	13.5	14.5	10.8	128	43

The broad, low lying heart, which gives a wide transverse diameter, will have a small angle, and the long heart, often found in the long, narrow chest, will have a wide angle. In the 277 cases, the range of this angle is from 23 to 63 degrees, showing the wide range that is present in the shape of the normal heart. The general average for the angle in this series is 43 degrees. An angle of 40 degrees or less is found in 41 per cent of these men. The long, narrow heart usually



TABLE 6—RELATION OF AREA TO DIAMETERS AND ANGLE IN CASES WITH A WEIGHT OF 59 KG

Area, Sq Cm	Height, Cm	Age	T D, Cm	L D, Cm	B D, Cm	Angle, Degree
110	165	25	11 5	13 5	9 5	48
111	157	23	12 3	13 2	9 6	44
111	160	24	12 4	13 3	9 8	46
111	163	22	12 1	13 8	9 7	41
112	165	29	12 6	13 6	9 6	40
112	168	24	12 6	13 7	9 4	41
112	175	30	12 8	13 5	9 7	54
112	178	22	12 3	13 5	9 8	48
112	178	27	12 5	13 7	9 9	47
113	168	26	12 8	13 8	9 7	40
113	170	30	12 8	13 5	9 8	47
113	173	24	12 7	13 6	9 8	49
113	173	27	12 9	13 4	9 8	41
113	173	28	12 7	13 9	9 9	40
113	175	19	12 9	12 6	10 1	42
113	175	21	12 8	13 6	9 8	49
113	175	27	12 7	12 9	10 3	44
113	178	30	14 0	12 7	9 1	29
114	165	23	13 5	13 9	9 7	32
114	170	23	13 6	13 0	9 9	40
114	170	23	12 7	14 1	9 7	54
114	173	28	12 7	13 9	10 3	38

TABLE 7—RELATION OF ANGLE TO DIAMETERS AND AREA

Angle Degrees	Cases	T D		L D		B D		Area	
		Range, Cm	Average, Cm	Range, Cm	Average, Cm	Range, Cm	Average, Cm	Range, Sq Cm	Aver, Sq Cm
23	1		14 2		14 3		10 3		130
24	2	13 4-14 3	13 9	14 2-14 5	14 4	10 3-10 4	10 3	126-133	130
26	3	13 6-14 3	13 9	12 0-14 1	13 3	9 4-10 4	10 1	112-134	122
27	2	13 7-13 9	13 8	14 0-14 3	14 2	10 0-10 7	10 4	126-131	129
28	2	13 8-14 0	13 9	13 8-14 3	14 1	10 1-10 2	10 1	127-132	129
29	3	13 5-14 0	13 8	12 7-14 1	13 6	9 1-10 2	9 8	113-129	122
30	3	12 1-13 5	13 0	13 5-14 6	14 0	10 3-10 7	10 4	112-125	119
31	4	12 2-13 5	12 8	13 7-14 3	14 0	10 4-10 6	10 5	112-116	114
32	7	13 1-13 8	13 5	13 0-14 9	14 1	9 6-11 2	10 3	113-135	121
33	7	12 3-13 9	13 5	13 8-14 8	14 2	9 7-11 1	10 5	114-130	125
34	17	11 6-14 2	13 0	12 9-14 9	14 1	9 9-11 3	10 5	110-136	121
35	9	12 4-13 8	13 0	13 5-14 7	14 2	10 1-10 9	10 6	113-130	121
36	10	12 7-13 8	13 2	13 0-15 1	14 2	9 6-10 9	10 3	110-136	123
37	11	11 9-13 7	13 0	13 5-14 9	14 1	9 5-10 8	10 2	110-132	119
38	11	11 6-13 6	12 9	13 0-14 7	13 9	9 5-10 8	10 3	108-132	119
39	6	12 6-13 7	13 3	12 9-14 6	14 2	10 4-10 8	10 6	111-135	121
40	19	11 3-13 8	12 4	13 2-15 2	14 0	9 5-11 1	10 2	106-128	116
41	13	11 3-13 7	12 9	13 2-15 1	14 1	9 4-10 8	10 2	111-134	120
42	12	11 4-13 8	13 1	12 6-14 9	14 2	9 9-10 8	10 5	113-130	123
43	9	11 4-13 7	12 8	13 6-15 2	14 2	10 3-11 2	10 7	112-132	120
44	12	11 0-13 8	13 0	12 9-15 1	14 1	9 6-11 3	10 3	107-133	120
45	12	11 4-13 6	12 9	12 8-15 2	14 1	9 7-11 3	10 4	108-130	118
46	8	12 4-13 7	13 2	13 3-14 9	14 3	9 8-11 4	10 7	111-137	122
47	15	10 1-13 7	13 0	12 4-15 0	14 1	9 8-11 1	10 4	108-132	121
48	14	11 1-13 5	12 4	13 3-14 9	14 0	9 5-10 8	10 3	109-134	117
49	9	11 5-13 5	12 9	13 6-15 0	14 3	9 8-11 3	10 5	113-131	120
50	11	11 1-13 9	12 6	13 6-15 2	14 4	10 1-11 1	10 6	112-135	121
51	4	11 8-13 6	12 5	13 3-14 2	13 9	10 2-10 8	10 6	108-123	114
52	8	11 9-13 8	13 3	13 9-15 1	14 5	10 1-11 2	10 7	118-130	125
53	6	11 3-13 3	12 3	13 4-14 8	14 1	9 6-11 0	10 4	112-126	116
54	10	11 1-13 9	12 6	13 6-15 2	14 4	10 1-11 1	10 6	112-135	121
55	5	11 1-13 3	12 0	13 1-14 5	13 9	9 6-10 7	10 1	106-117	113
56	5	10 6-13 5	12 1	14 0-15 0	14 5	10 2-10 8	10 5	111-133	119
57	3	13 2-13 4	13 3	14 1-15 0	14 5	10 2-11 6	10 8	123-132	128
58	2	12 1-12 8	12 5	13 9-14 3	14 1	10 5-10 7	10 6	113-114	113
60	1		11 6		13 5		9 8		106
63	1		11 6		14 5		11 0		122

TABLE 8—TELEROENTGEN MEASUREMENTS OF 277 NORMAL  
HEARTS OF SOLDIERS

No	Wt, Kg	Height, Cm	Age	T D, Cm	L D, Cm	B D, Cm	Area, Sq Cm	Volume Cc	Arch, Cm	Angle, Degrees
1	55	168	27	12 1	13 4	10 3	106	578	4 8	40
2	55	173	21	11 6	13 5	9 8	106	578	4 6	60
3	56	165	23	11 6	13 1	9 6	106	578	4 4	55
4	57	163	24	12 7	13 2	9 8	110	612	4 2	40
5	57	165	31	11 7	13 6	9 6	107	586	4 7	44
6	57	168	20	12 4	13 5	10 1	108	595	4 5	44
7	57	175	20	12 5	13 5	9 6	108	595	4 5	38
8	58	155	20	12 6	13 6	9 8	110	612	4 7	47
9	58	160	28	12 7	13 5	9 5	110	612	4 9	37
10	58	163	20	12 6	14 1	9 5	114	645	4 7	40
11	58	163	20	12 8	13 4	9 9	113	637	4 5	42
12	58	163	30	12 7	13 0	9 6	110	612	4 2	36
13	58	165	30	12 6	13 5	9 7	112	628	4 6	37
14	58	168	19	12 5	14 1	9 6	113	637	4 5	33
15	58	173	28	12 8	13 3	9 5	111	620	4 6	36
16	58	178	23	12 4	12 8	10 4	108	595	4 7	45
17	58	178	24	11 8	13 3	10 5	108	595	4 8	51
18	58	180	24	12 5	13 0	9 5	109	603	4 1	38
19	59	157	23	12 3	13 2	9 6	111	620	4 5	44
20	59	160	24	12 4	13 3	9 8	111	620	4 6	46
21	59	163	22	12 1	13 8	9 7	111	620	4 7	41
22	59	165	23	13 5	13 9	9 7	114	645	4 7	32
23	59	165	25	11 5	13 5	9 5	110	612	4 5	48
24	59	165	29	12 6	13 6	9 6	112	628	4 4	40
25	59	168	24	12 6	13 7	9 4	112	628	4 6	41
26	59	168	26	12 8	13 8	9 7	113	637	4 7	40
27	59	170	23	13 6	13 0	9 9	114	645	4 8	40
28	59	170	23	12 7	14 1	9 7	114	645	4 4	54
29	59	170	30	12 8	13 5	9 8	113	637	4 7	47
30	59	173	24	12 7	13 6	9 8	113	637	4 3	49
31	59	173	27	12 9	13 4	9 8	113	637	4 4	41
32	59	173	28	12 7	13 9	9 9	113	637	4 6	40
33	59	173	28	12 7	13 9	10 3	114	645	4 6	38
34	59	175	19	12 9	12 6	10 1	113	637	4 8	42
35	59	175	21	12 8	13 6	9 8	113	637	4 7	44
36	59	175	27	12 7	12 9	10 3	113	637	4 5	44
37	59	175	30	12 8	13 5	9 7	112	628	4 6	54
38	59	178	22	12 3	13 5	9 8	112	628	4 6	48
39	59	178	27	12 5	13 7	9 9	112	628	4 8	48
40	59	178	30	14 0	12 7	9 1	113	637	4 5	29
41	60	175	23	12 7	13 7	10 1	112	628	4 7	48
42	61	160	20	12 7	13 0	9 9	111	620	4 4	47
43	61	160	26	11 9	13 6	10 2	111	620	4 6	37
44	61	163	26	10 1	12 4	10 2	104	562	4 4	47
45	61	165	24	12 6	12 9	10 6	111	620	4 4	39
46	61	168	19	12 8	14 0	10 6	114	645	4 7	31
47	61	168	26	12 2	12 9	10 4	110	612	4 6	34
48	61	168	28	11 7	13 3	10 3	110	612	4 7	48
49	61	168	30	12 5	13 7	10 6	112	628	4 6	31
50	61	170	23	11 4	13 6	10 5	112	628	4 8	43
51	61	170	28	12 7	14 1	10 2	114	645	4 4	38
52	61	173	20	12 1	13 7	10 5	112	628	4 4	50
53	61	173	22	13 3	13 5	10 9	114	645	4 8	35
54	61	173	23	13 2	14 2	10 3	115	653	4 7	34
55	61	173	24	11 6	13 3	10 3	112	628	4 3	34
56	61	175	19	11 3	14 1	10 4	112	628	4 8	41
57	61	175	22	10 6	14 0	10 4	111	620	4 5	56
58	61	175	22	11 2	14 0	10 2	112	628	4 6	56
59	61	175	23	11 8	13 6	10 5	112	628	4 9	50
60	61	175	27	12 0	14 2	10 2	113	637	4 3	51
61	61	178	20	12 4	13 5	10 8	113	637	4 7	54
62	61	178	21	11 6	14 0	10 2	112	628	4 6	38
63	61	178	23	12 0	13 8	10 3	112	628	4 8	40
64	61	178	30	12 4	14 0	10 7	113	637	4 6	51
65	61	180	23	12 8	14 3	10 5	113	637	4 1	58
66	61	180	24	12 1	13 5	10 3	112	628	4 1	30
67	61	180	30	11 8	13 7	10 2	111	620	4 5	34
68	62	157	25	13 7	12 0	9 4	112	628	4 6	26
69	62	163	26	12 9	14 1	10 4	114	645	4 3	40
70	62	168	22	11 5	14 2	10 1	113	637	4 7	49
71	62	168	25	13 2	14 3	10 1	116	662	4 4	46
72	62	168	28	13 1	13 7	10 4	115	653	4 9	32
73	62	170	26	11 4	13 8	10 5	112	628	4 3	43
74	62	173	19	11 7	14 1	10 4	113	637	4 7	53
75	62	175	24	12 6	14 2	9 8	114	645	4 5	36
76	62	178	22	11 8	14 1	10 3	113	637	4 5	48

TABLE 8—TELEROENTGEN MEASUREMENTS OF 277 NORMAL  
HEARTS OF SOLDIERS—(Continued)

No	Wt, Kg	Height, Cm	Age	T D, Cm	L D, Cm	B D, Cm	Area, Sq Cm	Volume Cc	Arch, Cm	Angle, Degrees
77	62	178	23	12.2	14.0	9.7	114	645	4.6	37
78	62	178	28	11.1	13.5	9.8	112	628	4.1	48
79	62	178	29	12.6	13.8	9.7	113	637	4.7	45
80	63	155	26	11.3	13.4	10.3	112	628	4.8	53
81	63	160	30	11.8	13.5	10.4	112	628	4.7	55
82	63	163	27	11.4	13.5	10.2	112	628	4.6	45
83	63	163	23	12.1	13.6	10.1	113	637	4.3	35
84	63	168	26	11.8	13.2	10.0	112	628	4.0	41
85	63	170	22	11.5	13.8	9.9	112	628	4.5	40
86	63	170	22	13.6	13.0	9.6	113	637	4.7	32
87	63	170	23	11.7	13.9	10.1	113	637	4.3	42
88	63	170	24	11.7	13.5	10.4	113	637	4.9	54
89	63	173	20	13.2	14.2	10.4	115	653	4.9	32
90	63	173	22	11.2	14.4	10.2	114	645	4.7	50
91	63	173	23	11.6	14.5	10.1	114	645	4.7	48
92	63	173	23	11.8	13.6	10.1	114	645	4.6	34
93	63	173	25	11.5	13.9	10.4	114	645	4.4	48
94	63	173	25	12.0	13.9	10.4	114	645	4.4	34
95	63	173	26	12.7	13.8	10.2	114	645	4.5	34
96	63	173	28	12.0	14.1	10.2	114	645	4.5	41
97	63	175	22	10.6	14.4	10.4	114	645	4.7	54
98	63	175	27	11.1	14.5	10.7	115	653	4.3	55
99	63	175	27	11.4	13.7	10.5	113	637	4.6	42
100	63	178	19	11.0	13.9	10.6	113	637	4.3	44
101	63	178	23	12.2	13.8	10.5	114	645	4.7	31
102	63	178	24	11.1	13.6	10.1	112	628	4.4	50
103	63	178	25	12.9	13.9	10.4	114	645	4.9	40
104	63	178	27	12.0	14.2	10.5	114	645	4.5	45
105	63	178	28	12.1	13.9	10.7	114	645	4.0	58
106	64	168	20	11.7	14.0	10.4	114	645	4.8	40
107	64	168	22	12.6	13.9	10.4	114	645	4.6	37
108	64	170	21	12.3	13.8	10.5	114	645	4.5	33
109	64	170	23	11.7	14.6	10.6	114	645	4.8	50
110	64	170	24	12.6	14.6	10.6	116	662	4.8	46
111	64	173	21	12.4	13.8	10.6	114	645	4.4	43
112	64	173	24	12.0	14.8	10.6	115	653	4.5	56
113	64	175	22	12.7	14.8	10.8	116	662	4.6	56
114	64	175	26	12.6	14.4	10.7	115	653	4.9	35
115	64	175	26	12.4	14.6	10.5	115	653	4.4	35
116	64	178	23	12.8	13.8	10.7	115	653	4.6	48
117	64	178	25	12.4	14.5	10.4	116	662	4.7	45
118	64	178	25	13.1	14.4	10.6	116	662	4.8	45
119	64	178	26	12.3	14.7	10.7	115	653	4.3	50
120	64	180	23	13.7	14.3	10.7	117	671	4.7	40
121	64	180	26	13.8	14.4	10.3	117	671	4.5	37
122	64	180	27	13.3	14.3	10.4	116	662	4.6	31
123	65	165	23	12.6	13.8	10.8	115	653	4.4	36
124	65	168	23	13.2	13.4	10.7	115	653	4.5	34
125	65	168	27	13.2	14.0	10.0	116	662	4.9	32
126	65	170	22	12.8	13.9	10.8	115	653	4.3	35
127	65	173	19	13.1	13.7	10.9	116	662	4.6	46
128	65	173	25	12.6	13.4	10.8	115	653	5.0	38
129	65	173	26	13.4	13.9	10.6	116	662	4.6	43
130	65	175	20	12.5	13.9	11.0	116	662	4.7	53
131	65	175	26	13.0	13.8	10.8	116	662	4.7	43
132	65	178	36	12.9	14.1	10.8	117	671	4.8	39
133	65	180	23	11.4	14.0	11.2	115	653	4.4	54
134	65	180	27	13.3	13.9	10.6	117	671	4.6	55
135	65	184	23	13.7	14.3	10.9	117	671	4.7	40
136	65	184	28	12.8	14.1	10.3	116	662	4.6	47
137	66	170	23	13.7	13.5	10.5	116	662	4.5	54
138	66	178	23	12.9	13.8	10.6	116	662	4.4	45
139	66	178	26	12.2	14.3	10.3	117	671	4.5	55
140	66	180	26	13.6	13.9	10.5	116	662	4.5	39
141	67	160	22	12.9	13.7	10.7	116	662	4.5	38
142	67	168	24	13.4	14.0	10.5	117	671	3.8	34
143	67	168	26	13.6	13.8	10.6	117	671	4.7	33
144	67	168	29	12.8	14.0	10.2	118	679	4.5	40
145	67	170	26	13.6	14.1	11.2	121	705	4.6	52
146	67	170	26	12.6	14.3	10.6	119	688	4.7	34
147	67	173	29	12.9	15.0	11.2	123	723	4.8	49
148	67	178	21	13.6	14.7	10.8	123	723	4.6	42
149	67	178	22	12.9	14.5	10.3	121	705	4.6	44
150	67	178	23	13.5	13.9	10.4	119	688	4.7	45
151	67	178	31	13.0	13.9	10.7	119	688	4.6	44
152	67	180	24	13.4	14.3	10.8	122	714	4.6	41

TABLE 8—TELEROENTGEN MEASUREMENTS OF 277 NORMAL  
HARTS OF SOLDIERS—(Continued)

No	Wt, Kp	Height, Om	Age	T D, Om	L D, Om	B D, Om	Area, Sq Om	Volume Cc	Arch, Om	Angle, Degrees
153	67	180	27	12.1	15.0	10.1	121	705	4.5	58
154	67	183	31	13.6	14.1	10.4	121	705	4.6	26
155	68	165	22	13.0	13.9	10.6	119	688	4.0	18
156	68	168	26	13.0	11.1	9.7	121	705	4.7	33
157	68	170	20	13.3	14.2	10.6	122	711	4.4	39
158	68	170	22	13.4	14.0	10.4	122	711	4.8	45
159	68	173	18	13.8	14.3	10.8	123	723	4.0	33
160	68	173	22	13.5	13.9	10.7	120	697	4.4	30
161	68	173	25	13.4	14.5	10.1	123	723	4.2	46
162	68	173	25	13.6	14.2	10.8	123	723	4.7	51
163	68	173	29	12.7	14.0	10.2	120	697	4.7	40
164	68	175	25	11.0	14.3	10.8	118	679	4.3	52
165	68	175	26	13.3	13.8	10.7	121	705	5.1	47
166	68	175	26	12.7	14.2	10.8	121	705	4.6	48
167	68	178	21	13.7	14.6	11.2	125	741	4.7	47
168	68	178	27	13.4	14.5	10.0	123	723	4.6	45
169	68	178	29	13.4	14.3	10.8	121	732	4.5	52
170	68	178	29	13.6	14.4	11.2	125	741	4.9	17
171	68	180	20	13.1	11.1	10.6	123	723	4.7	57
172	68	181	28	13.3	14.7	10.9	125	711	5.0	46
173	68	183	10	13.6	11.0	10.5	121	723	4.3	41
174	60	168	27	13.5	14.7	10.6	125	741	5.1	47
175	60	168	31	13.6	14.2	10.3	123	723	5.0	37
176	60	170	21	12.9	14.1	10.3	122	711	4.5	37
177	60	170	26	13.5	14.1	10.2	123	723	4.6	29
178	60	173	20	13.6	11.3	10.8	121	732	4.6	45
179	60	175	20	12.7	14.7	10.4	122	711	5.1	35
180	60	178	21	13.5	11.6	10.8	121	732	4.7	38
181	60	178	24	11.4	14.6	9.9	119	688	4.2	51
182	60	180	23	12.9	11.4	10.5	123	723	4.3	31
183	60	180	26	13.1	14.4	10.9	121	732	4.1	36
184	70	168	27	13.5	14.4	10.3	121	732	4.8	13
185	70	170	22	13.5	14.7	10.1	125	741	4.5	40
186	70	173	22	13.5	14.0	10.2	126	750	4.1	41
187	70	175	23	13.5	13.8	11.2	121	732	4.4	10
188	70	175	21	13.1	14.5	10.5	125	741	4.7	33
189	70	175	25	13.5	14.6	10.4	125	741	1.5	39
190	70	175	28	13.4	14.4	10.6	125	741	4.6	50
191	70	175	28	13.5	14.6	10.3	125	741	4.8	30
192	70	175	28	13.6	14.8	10.5	127	750	4.6	52
193	70	178	22	13.1	14.6	10.8	125	741	4.7	40
194	70	178	23	13.3	14.7	10.8	126	750	4.0	42
195	70	178	23	13.6	13.0	11.2	121	732	5.0	52
196	70	178	25	13.4	15.0	10.2	127	750	4.1	57
197	70	178	31	13.4	13.8	10.5	122	711	4.8	41
198	70	178	31	13.3	14.4	10.1	123	723	5.0	47
199	71	168	21	13.5	14.2	11.3	126	750	5.1	19
200	71	170	27	13.4	14.4	10.3	126	750	4.0	49
201	71	170	27	13.7	14.0	10.0	126	750	4.8	27
202	71	173	26	11.6	14.3	11.0	122	711	4.5	63
203	71	173	29	13.5	14.0	10.4	127	750	4.7	36
204	71	175	21	12.0	15.1	10.1	127	750	4.2	52
205	71	175	26	13.3	14.3	10.5	125	711	4.5	53
206	71	175	32	13.4	14.6	10.5	126	750	4.4	48
207	71	178	27	13.4	14.7	10.8	127	750	4.8	56
208	71	178	28	13.6	15.2	11.1	120	777	5.0	10
209	71	178	29	13.1	15.2	11.2	128	768	4.6	43
210	71	178	30	13.2	14.8	10.4	127	750	4.6	54
211	71	180	28	13.4	14.6	10.6	127	750	4.6	43
212	71	183	19	13.3	14.3	10.5	126	750	4.8	35
213	72	168	30	13.4	14.8	10.2	127	750	4.0	47
214	72	170	26	13.8	14.3	10.2	127	750	4.5	28
215	72	173	24	13.5	14.5	10.4	127	750	4.6	44
216	72	173	28	13.4	14.2	10.1	126	750	4.7	24
217	72	175	21	13.7	14.1	10.2	127	750	4.0	37
218	72	178	24	13.5	14.8	11.1	128	768	4.5	33
219	72	180	29	13.3	14.0	10.5	128	768	4.5	42
220	72	180	31	13.6	15.0	10.4	120	777	4.6	47
221	72	183	25	13.5	15.2	11.3	130	786	4.5	45
222	72	181	25	13.8	14.6	10.4	130	786	4.6	42
223	73	170	26	13.7	14.7	10.6	130	786	4.0	41
224	73	170	32	14.2	14.3	10.3	130	786	5.2	23
225	73	175	25	13.5	14.7	10.1	129	777	4.7	50
226	73	178	26	13.4	14.5	10.1	128	768	4.7	35
227	73	183	30	13.5	15.1	9.9	129	777	4.7	41
228	74	178	23	13.7	15.2	10.1	130	786	4.5	36

TABLE 8—TELEROFNTGEN MEASUREMENTS OF 277 NORMAL  
HEARTS OF SOLDIERS—(Continued)

No	Wt, Kg	Height, Cm	Age	T D, Cm	L D, Cm	B D, Cm	Area, Sq Cm	Volume Cc	Arch, Cm	Angle, Degrees
229	74	178	28	13 5	14 9	10 3	129	777	5 2	48
230	74	180	24	13 8	14 8	10 3	130	786	4 8	36
231	74	180	27	13 8	14 7	10 5	130	786	4 6	52
232	74	180	30	13 9	14 8	10 3	130	786	4 5	34
233	74	183	31	13 8	15 1	9 9	130	786	4 7	44
234	75	163	31	13 7	14 7	10 4	130	786	4 7	42
235	75	168	23	13 9	14 1	10 2	129	777	4 6	29
236	75	173	28	13 7	14 3	10 4	130	786	5 0	33
237	75	173	29	13 6	14 5	10 6	130	786	4 8	42
238	75	178	24	13 5	14 5	10 8	130	786	4 6	54
239	75	178	24	13 9	14 3	10 7	131	795	4 9	27
240	75	180	24	13 5	14 3	10 5	129	777	4 2	42
241	75	180	29	13 5	14 9	10 6	130	786	4 6	52
242	75	180	29	13 6	14 5	10 6	130	786	4 2	37
243	75	180	30	13 8	14 6	10 5	130	786	5 0	35
244	75	180	31	13 7	14 2	10 9	130	786	4 9	36
245	75	184	27	13 6	14 4	10 7	130	786	4 7	42
246	75	184	28	13 5	14 8	10 8	131	795	4 8	44
247	76	168	23	13 7	14 9	10 8	132	804	4 4	37
248	76	173	23	13 6	14 6	10 7	131	795	5 1	34
249	76	178	23	13 4	14 9	10 6	131	795	4 6	49
250	76	178	31	13 5	13 9	10 8	129	777	4 5	41
251	76	180	23	13 8	14 5	11 3	133	813	4 4	44
252	76	180	29	13 7	14 7	10 8	132	804	4 6	50
253	76	180	29	13 7	15 0	10 8	133	813	4 6	50
254	76	184	23	13 6	14 7	10 8	132	804	5 0	47
255	77	165	23	14 3	14 5	10 3	133	813	4 9	24
256	77	168	26	13 7	14 9	10 9	133	813	4 9	34
257	77	173	25	13 8	14 0	10 5	131	795	4 5	34
258	77	173	28	13 4	14 7	10 7	132	804	4 5	38
259	77	175	25	13 8	14 5	11 3	133	813	4 9	34
260	77	178	24	13 7	14 5	10 9	132	804	4 8	43
261	77	178	27	13 6	14 3	10 0	130	786	4 4	38
262	77	180	27	13 4	14 9	10 8	132	804	4 5	47
263	78	173	26	14 0	13 8	10 1	132	804	4 7	28
264	78	178	27	13 5	15 0	10 6	133	813	4 5	56
265	79	170	25	13 7	15 2	10 8	135	832	5 0	39
266	79	178	20	14 2	14 9	9 9	136	841	4 5	34
267	79	183	25	13 2	14 5	11 6	132	804	4 6	57
268	79	184	25	13 5	14 0	10 7	129	777	4 3	38
269	80	178	25	13 9	15 2	11 1	135	832	4 4	50
270	80	180	30	13 5	14 6	11 3	134	823	5 1	46
271	81	165	26	13 5	14 9	11 2	125	832	4 7	32
272	81	178	28	14 3	13 9	10 3	134	823	4 8	26
273	81	180	30	13 3	14 5	10 8	134	823	4 6	48
274	82	173	25	13 5	14 8	10 7	134	823	4 5	41
275	83	178	25	13 8	14 5	10 9	135	832	5 0	32
276	83	178	29	13 6	15 1	10 9	136	841	4 4	36
277	84	184	38	13 7	14 9	11 4	137	850	4 5	46

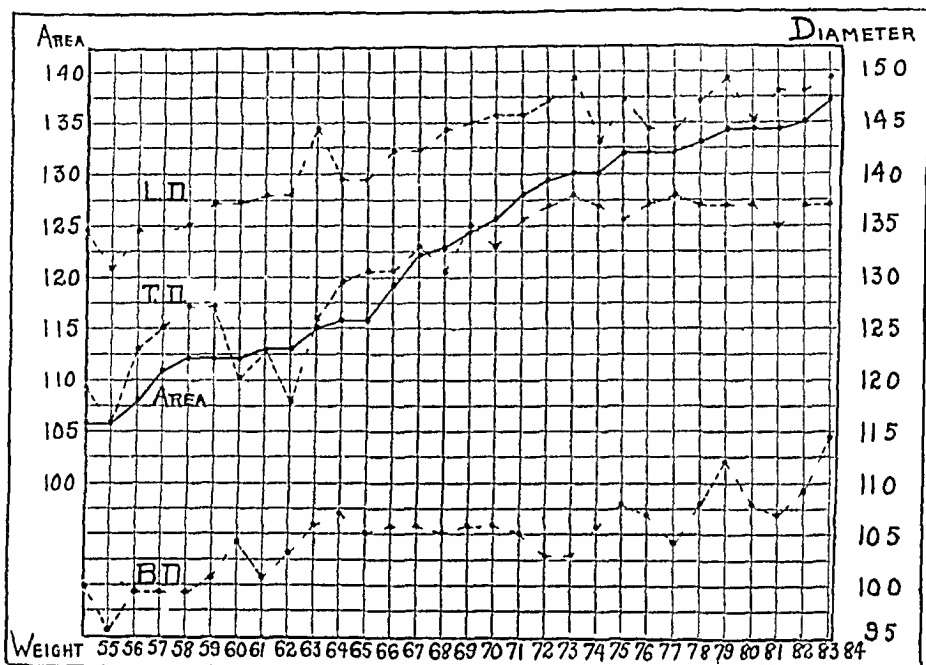
occupying a more median position in the chest, was present in 20 per cent of the men. In these men the angle measured 54, 55, 56, 60 and 63 degrees, respectively.

No evidence has been found in this study that the hearts of soldiers are enlarged after active military service. The average measurements for the diameters and area agree closely with the normal figures of Dietlen and Bardeen.

The individual measurements for area are well within the normal range.

The individual measurements for the transverse diameter, in cases with the same body weight, show considerable variation, and emphasize the danger of basing an opinion of size on the determination of this diameter alone.

A consideration of the shape of the heart is important in any questionable enlargement. If the area is not measured, the angle formed by the transverse and long diameters can be an aid.



Relation of area and diameters of heart to body weight. T D = transverse diameter, L D = long diameter, B D = broad diameter.

Hearts of soldiers who have performed active service are largely of the broad type, with a wide transverse diameter. Only a small percentage of the men had hearts of the narrow type, with a small transverse diameter and a broad angle.

# TELEROENTGEN ESTIMATIONS OF HEART SIZE IN CASES OF EFFORT SYNDROME \*

BERTNARD SMITH, M D

LOS ANGELES

Silhouette measurements of the heart were made in 119 cases of effort syndrome by the teleroentgen method. The same technic was followed throughout the work. All exposures were taken with the subject in the standing position, with the target 6½ feet from the plate. When in position, facing the plate, the subject was told to take a deep breath and then empty his lungs as completely as possible. Following this, he took a half breath and held it for the exposure, which was from 1½ to 4 seconds' duration, varying with the weight of the individual and the thickness of the chest wall. This method was adopted because the directions were easily carried out, and it gave satisfactorily uniform results.

From the plates thus obtained the following measurements were made

1 Ml Maximum left border

2 Mr Maximum right border

From the sum of these was obtained the maximum transverse diameter T D

3 L D Maximum long diameter from the right auricular notch to the most distant apical border

4 B D Maximum broad diameter, measured at right angles from L D to the most distant borders

5 The angle formed by the long and transverse diameters

6 The diameter of the aortic arch

7 The parallel ray silhouette area<sup>1</sup> was obtained by the planimetric method and from this was calculated the volume by the Bardeen formula<sup>2</sup>

In the cases studied, the men who gave a history of symptoms present before entering the army showed a lower general strength and a poorer physical development than did those patients whose symptoms developed during active military duty. The cases are tabulated in this report into two groups, according to the time of onset of the general effort syndrome symptoms.

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\* Report from Studies made on the Cardiovascular Service, U S Army General Hospital No 9, Lakewood, N J

1 Bardeen, C R Am J Roentgenol 4 604, 1917

2 Bardeen, C R Am J Anat 23, 423, 1918

## 1 CASES WITH SYMPTOMS BEFORE MILITARY SERVICE

The sixty-nine cases of this group are arranged in Table 1 by weight. Bardeen<sup>2</sup> has stated that the transverse diameter is about 70 per cent less in the standing than in the recumbent position, and about half of this difference is found between the sitting and recumbent positions. These differences have been taken into consideration in comparing measurements with the Dietlen and Bardeen tables for normals.

TABLE 1—HEART MEASUREMENTS IN CASES OF EFFORT SYNDROME WITH SYMPTOMS PRESENT BEFORE MILITARY SERVICE

Weight, Kg	Cases	Height, Aver., Cm	Age, Aver age	T D, Cm	L D, Cm	B D, Cm	Area, Sq Cm	Angle, Degrees		Arch, Cm
								Range	Aver	
45-40	2	171	28	8.8	13.2	8.9	90	60-65	62.5	4.1
50-54	8	171	25	9.9	13.3	9.0	107	41-63	53.0	4.5
55-59	18	172	24	10.8	13.5	9.2	111	30-65	47.0	4.5
60-64	22	171	27	12.2	13.2	9.5	112	32-61	44.5	4.5
65-69	13	174	26	12.1	13.5	9.6	113	36-58	45.1	4.6
70-74	4	174	25	12.4	14.3	9.7	122	38-60	47.8	4.6
75-84	2	176	23	11.2	14.7	9.7	123	41-59	43.0	4.4

When the measurements for the transverse diameters are compared with the Dietlen<sup>3</sup> and Bardeen<sup>4</sup> tables for normals, the effort syndrome cases give an average diameter that is 0.68 cm less than the normal average. Meakins and Gunson<sup>5</sup> have reported measurements by the orthodiagraphic method of fifty cases in which they found the transverse diameter averaged 0.70 per cent less than the normal as given in Dietlen's tables. When the heart volume is compared with the Bardeen table, the effort syndrome cases give an average that is 9.8 per cent less than the normal, when arranged according to the subject's weight.

Measurements were made on 277 men who had had at least three months active duty in the fighting line, and who had gone through their training and forced marches without symptoms. The full report is reserved for a separate publication, but a summary of the measurements is given in Table 2 for comparison, since the technic followed was the same as with the cases in this report.

When the measurements for the effort syndrome cases are compared with this series of normal hearts, the transverse diameters for the sixty-nine patients average 0.98 cm less. However, when the volumes are compared, the average difference for the effort syndrome cases is 10.1 per cent less, as arranged by weight, than for the men who had performed full duty.

<sup>3</sup> Dietlen, H. *Deutsch Arch f klin Med* 88:55, 1907

<sup>4</sup> U. S. Army X-Ray Manual

<sup>5</sup> Meakins, J. C., and Gunson, E. B. *Heart* 7:1, 1918

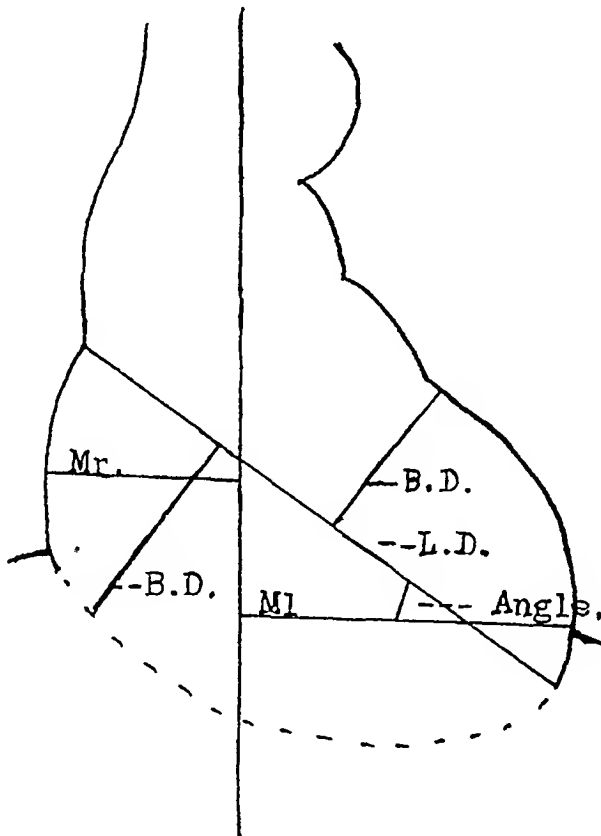


TABLE 2—HEART MEASUREMENTS OF SOLDIERS AFTER MILITARY SERVICE

Weight, Kg	Cases*	Height, Aver, Cm	Age, Aver- age	T D, Cm	L D, Cm	B D, Cm	Area, Sq Cm	Angle, Degrees	
								Range	Average
55-59	40	170	25	12.6	13.4	9.9	111	29-60	41
60-64	82	168	24	11.9	13.6	10.2	113	26-56	43
65-69	61	178	27	11.5	14.1	10.6	118	26-57	41
70-74	50	177	27	13.4	14.7	10.7	127	24-63	42
75-79	35	176	27	13.7	14.5	10.6	129	24-56	41
80-84	9	179	29	13.7	14.7	10.9	135	26-50	40

\* These men were orthopedic cases in U S Army General Hospital No 9

The silhouette of the long, narrow heart was found in 24.6 per cent of the sixty-nine cases. This does not include the rounded, flask shaped shadow with a small transverse diameter. The low, broad type of shadow was found in 29.0 per cent of the cases. The angle formed by the long and transverse diameters is small in the low, broad heart



and widens as the type approaches the narrow form. In Table 1 are given the range and average of this angle for the different weight groups. For the sixty-nine cases the range is from 30 to 65 degrees, with a total average of 49.6 degrees. The range of this angle for the narrow types of hearts is from 52 to 65 degrees, with an average of 57.6 degrees.

The majority of the sixty-nine cases were of the type of chronic physical invalidism,<sup>6</sup> and had a low weight. If the weights are compared with the normal figures for the same age and height we obtain the following

Weight 45-49	average 254 per cent below normal
Weight 50-54	average 170 per cent below normal
Weight 55-59	average 186 per cent below normal
Weight 60-64	average 41 per cent below normal
Weight 65-69	average 10 per cent below normal
Weight 70-74	average 11 per cent above normal
Weight 75-84	average 17 per cent above normal

Of the sixty-nine patients, 65 per cent were below their normal weight, as given in the standard tables for age and height. This low weight in these men was associated with poor skeletal strength that had persisted for a number of years and often since childhood. Bardeen<sup>7</sup> states that "the size of the heart is determined rather by the development of the skeletal musculature than mere body weight, although the latter alone is subject to direct measurement." If the small heart of the effort syndrome is part of the picture of poor muscular development, later statistics will be of interest from those patients who have been developed to take up more active civil work.

TABLE 3—HEART MEASUREMENTS IN CASES OF EFFORT SYNDROME WITH SYMPTOMS DEVELOPING DURING MILITARY SERVICE

Weight, Kg	Cases	Height, Aver., Cm	Age, Aver- age	T D, Cm	L D, Cm	B D, Cm	Area, Sq Cm	Angle, Degrees		Arch, Cm
								Range	Aver	
50-54	4	162	23	11.1	12.8	9.6	107	43-61	48.8	4.2
55-59	7	174	24	10.9	13.3	9.6	109	30-54	45.8	4.5
60-64	15	171	24	11.7	13.9	9.7	112	31-48	43.5	4.5
65-69	13	174	25	12.5	13.7	9.8	118	27-58	43.7	4.7
70-74	11	172	26	12.7	14.3	10.4	124	34-61	41.0	4.9

## 2 CASES DEVELOPING SYMPTOMS DURING MILITARY SERVICE

No cases are included in this report in whom effort syndrome symptoms developed after an infectious disease. Measurements from fifty cases, in which the symptoms were of recent origin, are given in Table 3 as grouped by weight. The transverse diameters have a total average difference of 0.28 cm when compared with the Dietlen and Bardeen tables. The volume average is 21 per cent less than the Bardeen figures for normal when arranged by weight. When the fifty cases are compared with the normals of Table 2, the transverse diameters of the effort syndrome cases have an average that is 0.54 cm. less and an average volume that is 27 per cent below the average for

6 Campbell, C. M. J. A. M. A. 71:1621 (Nov. 16) 1918.

7 Bardeen, C. R. Anat. Rec. 10:176, 1915.

the normals The long, narrow type of heart shadow is found in only 20 per cent of the cases with recent onset of symptoms, while the broad heart is seen in 50 per cent The range for the angle in this group is from 27 to 61 degrees, with an average of 44.7 degrees for the fifty cases

A comparison of the weights of the men in this group with the normal figures for height and age gives an equally sharp contrast to those of Group 1

Weight 50-54	average	60	per cent	below normal
Weight 55-59	average	100	per cent	below normal
Weight 60-64	average	116	per cent	above normal
Weight 65-69	average	06	per cent	above normal
Weight 70-74	average	74	per cent	above normal

The weights range from 88 to 109 in per cent of normal, with a total average for the 50 cases of 102.3 per cent

#### SUMMARY

Cases of effort syndrome, in which symptoms have persisted for a long period of time, have smaller hearts than normal when compared by measurements of the transverse diameter, area and volume

The narrow, long heart, or "drop-heart," is not the predominant type found The small heart may vary in form as widely as the normal, and usually shows a decrease in the transverse, long and broad diameters

The smaller measurements are found in those men whose skeletal musculature has never been developed normally

The patients studied at Lakewood, who acquired the effort syndrome during active army duty, show silhouette measurements that are well within the normal range for area and volume The transverse diameters average slightly less than normal In such hearts the long diameter is usually slightly increased

The angle formed by the transverse and long diameters shows a greater average width in the men whose symptoms have been of long duration than in the normals and in the cases with a more recent onset Those individuals, whose silhouette gave this wide angle, had also a long, narrow chest wall

I wish to express my indebtedness to Lieut F W Keyes for his assistance in constructing the apparatus for the teleroentgen studies, and to Lieut Milton H Glover for his cooperation in the roentgen-ray technic

# PURULENT TYPHOID MENINGITIS

## REPORT OF A CASE

E A BAUMGARTNER PH D MD AND H H OLSEN MD  
HALSTEAD KAN

Meningitis due to the *B typhosus* is a relatively rare disease Cole collected the cases recorded up to 1904 We have been able to find twenty-three cases recorded in the literature since that time

In addition to reviewing the cases reported by Cole, we wish to report a case in which cholecystitis and otitis media were additional complications We had the opportunity of doing a necropsy in this case thus making an anatomic study of the complications possible The findings of the meningeal complication and of a pure typhoid culture comply with all of Cole's requirements for the diagnosis of purulent meningitis

## REPORT OF CASE

CASE 3494—R A, aged 6 admitted to the Halstead Hospital Oct 12 1919, with complaint of headache, fever and abdominal pain

*Family History*—Negative One brother living and well The brother later developed typhoid fever and was a patient in the hospital Positive Widal no complications

*Personal History*—When 3 years old, the patient had swollen glands on both sides of neck, not associated with pain or redness but tender These swellings disappeared in about four weeks Patient had an acute tonsillitis when 5 years of age

*Present History*—The patient had an attack of diarrhea October 6 On the afternoon of the seventh, he complained of abdominal pain Two days later he was seen by a physician On the second day the patient's temperature was 102 F October 12 it was 105 F

The boy was brought to the hospital the evening of October 12 He was seen for the first time by our staff His temperature was 105.8 pulse 150, leukocyte count 9,000 His head, neck and chest were negative His abdomen was somewhat distended and tender The spleen was not definitely palpable nor were any other masses found There was painful urination The urine was slightly clouded and showed a trace of albumin, otherwise it was negative

During the night he was restless, thirsty expelled much flatus and several watery stools with mucus The next day the patient was delirious the temperature remaining above 104 F the pulse rate was about 120 On the following three days he was quite restless, at times passing urine and feces involuntarily He was delirious and picked at the bed clothes At times he was noisy complained of stiffness of his legs pain in his throat and difficult deglutition His temperature slowly came down The spleen was now definitely palpable but at no time were rose spots noted

On the sixth day his temperature reached 101 F He had some epistaxis on this day and later passed several dark red stools which showed blood He seemed more quiet and rational, but complained of pain on voiding urine and when his bowels moved During the following days his temperature remained between 100 F and 102 F pulse 104 to 130 On the eleventh day,

the temperature again rose to 104 F, pulse was about the same. Voiding and passing of stools was painful, the patient was restless and crying. A mass, soft and fluctuating, had been noticed in the right subcostal region two days earlier. This had increased until it reached the level of the umbilicus and was plainly visible. The leukocytes numbered 17,400.

*Diagnosis*—Acute cholecystitis was diagnosed.

*Operation*—In the afternoon an operation was performed. The gallbladder was very much enlarged, extending below the umbilicus, its vessels were congested, walls thin and almost transparent. About 70 c.c. of a rather thin, slimy, greenish bile was evacuated, and then a greenish yellow fluid was found. Smears showed only a very few epithelial-like cells. The culture was negative.

*Subsequent Course*—During the next three days, the temperature ranged from 103 to 104.5 F, pulse, 120 to 134. The patient was restless, crying and very thirsty. On the sixteenth day, his neck was stiff and the head was drawn back. There was involuntary passage of urine and stools. The throat contained much phlegm. A yellowish discharge came from the left ear. The pulse ranged between 116 and 132. On the evening of the seventeenth day, at 6 p. m., the patient had a convulsion, lasting about twenty-five minutes, during which the temperature rose to 107 F, pulse to 140. The pupils were markedly dilated. The patient was cyanotic.

The next day the patient was restless, the muscles of the face were twitching, temperature 103 to 106 F, pulse, 120 to 150, neck stiff, Kernig positive, knee jerks somewhat increased. Spinal puncture showed fluid under pressure, cloudy, about 15 c.c. was removed. Cell count, 400, mostly mononuclears. Smear gram-negative, short bacilli, slightly motile, mononuclear cells. Culture, motile bacilli, gram-negative.

On the eighteenth day, the patient was quieter, cyanotic, temperature, 105 to 105.5 F, pulse weak, 140 to 156, but difficult to count, blood tinged mucus in throat.

Patient died at 2 p. m.

A spinal puncture at 2:30 p. m. showed fluid not under increased pressure, turbid, about 15 c.c. Cell count, 400, mostly mononuclears. Smear gram-negative, short bacilli, Ross Jones slightly positive. Culture hanging drop, motile bacilli, gram-negative.

*Autopsy*—Four p. m. Body, that of a white boy, about 5 or 6 years old, fairly good build, nutrition fair, small bruises over left internal malleolus, and external surface right ankle. Operation wound with rubber tube drain in upper right abdomen. Pupils, 3 mm., equal.

*Brain*—Meninges somewhat injected, on removing dura brain surface of frontal lobe covered with thin, pale yellow, cloudy film (Figs 1 and 2). A collection of pus (?) in posterior fossa between cerebellum and medulla.

*Abdomen*—No free fluid in abdomen. Omentum well walled about gallbladder region.

*Stomach and Intestines*—About 36 inches below pylorus, a short intussusception, of about 2 inches, existed. Below this, a large amount of tarry stool filled about 2 feet of the intestine. On section, no ulcers observed, except near ileocecal valve, where the mucosa was markedly reddened, and studded with minute ulcerations. Lymph nodes in mesentery, especially near intestine, are markedly enlarged, measuring 1 cm. and more in length and from 0.5 to 0.7 c.c. in thickness.

*Liver and gallbladder* appeared to be quite normal. Gallbladder shrunk to about 6 cm. in length and in diameter to the size of the rubber tube drain placed at operation. Wall not thickened. Liver on section normal. Cystic and common duct appear normal in size and structure, no obstruction present.

*Spleen*—Increased in size 10.5 by 8.5 by 4, weight, 146 gm. Splenic nodules show prominently in section.

**Kidneys** Fatty capsule, comparatively thin, capsule strips easily from both. Left kidney, 10 by 6.5 by 4.5, weight, 163 gm. Right kidney, 9 by 5 by 3, weight, 84 gm. Cortex about from 5 to 8 mm thick in both kidneys. Pelvis both markedly dilated as are the ureters at the lower end. Both stood out prominently, measuring about 8 or 10 mm diameter from pelvic brim to the bladder. Probe passed easily to the bladder.

**Heart and Lungs** Not taken.

**Microscopical** Brain shows meninges (except dura) markedly infiltrated with polymorphonuclear leukocytes and other cells (Fig 3). This infiltration follows the vessels only a short distance into the cortex.

On closer examination it is seen that many of the cells in the meninges are not polymorphic cells but large plasmatike cells some about 15 microns in diameter, markedly vacuolated with small reddish stained inclusion particles, possibly red cells, the nuclei more or less eccentrically placed, rather



Fig 1—Photograph of left surface of brain

large, irregular shaped, with a small amount of chromatin material. These cells are not numerous (Fig 4).

What is particularly striking in a cursory examination is that the cellular infiltration about the blood vessels is markedly less dense than elsewhere; this is especially true of the veins (Fig 3). The mononuclear cells are about equally distributed in the perivascular areas and elsewhere. In the densely cellular areas are numerous small nuclear bodies from 3 to 4 microns in diameter, quite uniformly stained, with no darker stained chromatin masses.

The most common cells besides the polymorphonuclears are plasma-like, with pale staining, more or less vacuolated cytoplasm. The nuclei are large, round, eccentric in position, usually one or two nucleoli, and very little other chromatin.

There is remarkably little perivascular infiltration in the cortex, and a surprising decrease about the blood vessels in the membranes.

The area at the base of the cerebellum which in gross appeared as pus, showed cellular infiltration as described above. Despite a careful search, no definite bacilli could be found in 10 micron sections.

**Kidneys** Markedly dilated convoluted tubules, capillaries congested in cortex, glomeruli only slightly enlarged. Convoluted tubules show granular epithelium, nuclei stain quite well, occasional red blood cells in tubules, no casts, but occasional desquamated epithelial cells.

**Spleen** Shows quite large nodules, rather increased vascularity. The splenic sinuses are large, dilated, empty. The pulp shows many red blood cells.

**Mesenteric Lymph Nodes** Large, the one sectioned measuring about 1 cm in diameter, with a very large artery and vein in the center. Most of the section shows lymphoid tissue with some increase of connective tissue and congested vessels. One large area, macroscopically visible, is necrotic, has numerous polymorphonuclear cells with small necrotic nuclei, and pink staining fibrous debris.

**Liver** Shows quite large sinuses with numerous red blood cells. About the central veins, the hepatic cells appear smaller, but stain well.

We did not have all the mediums necessary for the proper isolation of typhoid bacilli, so we sent a subculture of the spinal fluid taken the day before death to Dr. Noble Sherwood, whose report was, in part, as follows:

"The culture as received contained two organisms, a gram-negative rod and a gram-positive spore producer. I plated them immediately, and beg to report the gram-negative rod as a slightly atypical strain of *B. typhosus*. Its reaction to the gram stain is typical, but the motility is so slight as to be negligible. I have repeatedly observed that freshly isolated strains of *B. typhosus* were frequently either nonmotile, or slightly motile for several generations after isolation, and then they would suddenly become actively motile. This is more especially true when organisms have been isolated from the blood stream, rather than from feces.

"The strain sent in by you does not produce any acid or gas in saccharose, this is typical. It gives acid, no gas in dextrose and mannite, these reactions are typical. It seems to show a tendency to acidify lactose, this is an atypical reaction. However, this strain is identical in its action on lactose as in a European strain of *B. typhosus* we have under observation. The reaction in gelatin shows no liquefaction, which is typical for *B. typhosus*.

"Now, the agglutination test with a polyvalent antityphoid serum shows agglutination in dilution of 1:3,000. The other laboratory strains, such as the New York Board of Health and the Bender strain, show agglutination in 1:8,000 and 1:10,000 dilutions. We have isolated quite a number of strains, however, that show agglutination in dilutions higher than your strain and less than the other strains.

"I feel no doubt that the organism you are working with is *B. typhosus* and apparently quite similar to the European strain which we have been working with."

To verify these findings, we also sent a subculture to Dr. F. J. Hodges, Department of Pathology, Washington University Medical School, St. Louis, and append part of his report. (Unfortunately, both specimens sent seem to have been contaminated, as in our earlier cultures we found only one gram-negative short bacillus. Our later cultures here were contaminated by a gram-positive, large, thick bacillus.)

"There are three organisms in the original cultures. One a gram-positive spore former overlooked in the first smears because of the great preponderance of gram-negative bacilli of two morphologic types. One gram-negative bacillus is very short and fat. The other, recovered from isolated colony on agar plate, is nearly twice as long, and little, if any, wider. The gram-positive organism was discarded. Both gram-negative strains gave typical sugar results for typhoid (when mixed with the gram-positive spore former, the sugar reactions were atypical) and both gram-negative strains are agglutinated by the stock typhoid serum. In cross agglutination tests, Para 'A' and Para 'B' and the dysenteries, the results are widely different for the two organisms, indicating that both morphologically and serologically we have here two types of typhoid bacillus.

'These two types labeled and sent to us as BI and BII agglutinated the stock typhoid serum at 1:6000 and 1:24000 respectively. BII was agglutinated by various low dilutions of both Para A and B serum, and by Flexner's serum but neither by Shiga bacillus serum in any concentration.

We had begun a thorough collection of the reported cases of typhoid meningitis intending only to summarize the purulent cases since Cole's paper<sup>1</sup>. Then we found Bayne-Jones's<sup>2</sup> article published in 1917 although apparently prepared in 1915. We have found only a few cases that he has not noted and have completed the table for comparison with Cole's cases.



Fig 2—Photograph of a cross section of the left half of the brain

McCrae<sup>3</sup> cites a case of typhoid fever, diphtheria and acute encephalitis. The diphtheria bacillus was found early in the disease but disappeared after a few days; the blood culture gave a pure typhoid growth and the Widal was positive. The necropsy report showed a reddish sphenotemporal lobe and thrombosed vessel in this part but unfortunately no cultures were made from the brain.

Schwartz reviewed some of the cases reported by Cole and thinks that contamination of the spinal fluid may take place through the blood which is known to contain the *B. typhosus*. He would exclude these

1 Cole, R. Typhoid Meningitis. Johns Hopkins Hosp. Rept. 12:299, 1904.

2 Bayne-Jones, S. Typhoid Meningitis. Report of a Case. Am. J. M. Sc. 154:55, 1917.

3 McCrae, I. Two Unusual Occurrences in Typhoid Fever: Acute Encephalitis and Perforation of the Sigmoid Flexure. Lancet 1:712, 1905.



# SUMMARY OF CASES OF PURULENT TYPHOID MENINGITIS

Author	Sex	Age	Diagnosis	Meningeal Symptoms	Onset of Meningeal Symptoms Day	Day of Death	Laboratory Findings	Necropsy	Bacteriologic Data
Crouchet et Buard, 1902	M	13	Typhoid		37th	37th	35th day spinal fluid turbid culture pure typhoid	None	
McCræ 1905	M	22	Typhoid	Drowsy, delirious	8th	14th	13th day, Widal positive, blood culture, pure typhoid	Temporal lobe, thrombosed vessel, small cell infiltration and perivascular	Incomplete
Delille, 1905	F	9	Typhoid		21st	28th	Spinal fluid turbid, culture, pure typhoid postmortem same	Purulent meningitis usual typhoid lesions	
Staubb 1907	M	22	Typhoid	Headache Stiff neck Kernig	3d 17th	22d	7th day spinal fluid negative 10th day Widal 1:100 21st day spinal fluid cloudy, polymorphonuclears, agglutinated typhoid bacilli 1:100, culture pure typhoid, agglutinated by typhoid serum	Purulent meningitis, few typical typhoid lesions	Good
Henry and Rosenberger 1908	M	34		Delirium	3d	9th	7th day, spinal fluid negative 9th day same, polymorphonuclears typhoid like bacilli agglutinated by known serums 1:40 blood culture same postmortem spinal fluid same	Purulent meningitis no intestinal lesions	Good
Southard and Richards 1908	M	31	Typhoid	Unconscious	5th	7th	Postmortem spinal fluid culture, pure typhoid, agglutinated by typhoid serums 1:5,000	Polymerphonic infiltration of pia mater no intestinal lesions	Good
Lavenson, 1909	F	26	Typhoid				Spinal fluid turbid, culture, pure typhoid	Purulent meningitis no intestinal lesions	Good
Symmers and Wilson 1909	M	37		Delirious	10th	14th	14th day, Widal positive, postmortem spinal fluid, purulent, culture, pure typhoid	None	
Schwartz, 1910	M	8	Typhoid	Stupor	14th	19th	15th day, Widal negative, 19th day, spinal fluid turbid, lymphocytes, culture pure typhoid, agglutinated by typhoid serums 1:100	None	Good Spinal fluid obtained before death
Lemierre et Joltrain, 1912	M	47	Otitis meningitis	Vertigo Delirious	2d 4th	7th	3d day spinal fluid turbid, polymorphonuclears 99%, culture, pure typhoid, agglutinated by typhoid serums 1:10 spinal fluid agglutinates typhoid bacilli 1:20	Purulent meningitis usual typhoid lesions	Good
Lyall, 1912	F	4 mo		Opisthotonus Improved Unconscious	1st 6th 34th	36th	6th day, spinal fluid clear, 9th day spinal fluid culture negative 17th and 19th days same, 34th day, cloudy polymorphonuclears culture, atypical typhoid, agglutinated by known typhoid bacilli, after many generations	Purulent meningitis, large mesenteric glands,	Good
Isesieu et Muchand 1912	M	41	Typhoid		25th	29th	Spinal fluid turbid culture pure typhoid blood culture same	Purulent meningitis, no intestinal lesions	Good

O'Carroll and Purser, 1912	M	9		Rigor	17th	22d	5th day, Widal positive, 8th day spinal fluid negative, 21st day, spinal fluid turbid, 1,100 cells 68% polymorphonuclears, culture, pure typhoid, agglutinated by typhoid serums 1:50	Purulent meningitis, no spleen or intestinal lesions	Good
Planebe et Lombard, 1914	M	2	Typhoid		24th	27th	Spinal fluid purulent, culture, pure typhoid	Purulent meningitis, no intestinal lesions	Fair
	M	8	Typhoid		35th	36th	Spinal fluid culture, pure typhoid postmortem culture of lungs, pneumococcus	Purulent meningitis, usual typhoid lesions	
d'Oelsnitz et al 1915	M	23	Infraorbital wound	Rigor	18th	24th	10th day Widal 1:10, 20th day, spinal fluid cloudy, increase in cells culture pure typhoid, agglutinated by typhoid serums 1:100, 21st day, Widal positive	None	Good
Ortoconni et Amemille 1915	M	28		Stupor Coma	5th 8th	8th	5th day, blood culture, pure typhoid, 8th day, spinal fluid clear, increase in cells culture, pure typhoid, agglutinated by typhoid serums	Congestion of brain, increase of fluid, usual intestinal lesions	Good
Robinson 1915	M	55	Meningitis	Coma	1st	4th	2d day, spinal fluid turbid, increase cells culture, pure typhoid, 3d day, same agglutinated by typhoid serums 1:50, serum from this agglutinated known typhoid 1:2,000	None	Good
Bayne Jones, 1915	F	19	Typhoid	Violent headaches Improved Kernig positive	10th 11th 19th	28th	21st day, spinal fluid negative, 22d day, blood culture pure typhoid, 24th day, spinal fluid turbid, increase in cells, culture, pure typhoid, agglutinated by typhoid serum 1:3,200	Purulent meningitis, usual typhoid lesions	Good
Konnamour et Mervgenis, 1917	F	25	Typhoid	Stupor Convulsion	14th 24th	28th	6th day, Widal negative, 10th day, spinal fluid negative, 15th day, Widal 1:50, blood culture pure typhoid, agglutinated by typhoid serums, 23d day, spinal fluid, increase in cells, 60% lymphocytes, 26th day, spinal fluid turbid no agglutination with typhoid bacilli, 28th day, spinal fluid purulent 88% polymorphonuclears culture, pure typhoid, agglutinated by typhoid serum 1:250, agglutinated typhoid bacilli 1:1,000	Purulent meningitis, more anteriorly spleen negative usual typhoid lesions	Good
Merklen et Gautier, 1917	M	32	Typhoid	Comatose, Kernig, involuntaries	?	?	Spinal fluid, many polymorphonuclears culture pure typhoid, agglutination positive	Purulent meningitis	Good
Cintra, 1918	M	33		Comatose	3d	4th?	4th day, Widal negative blood culture pure typhoid spinal fluid increase polymorphonuclears, culture, pure typhoid, agglutinated by typhoid serums 1:100 and 1:8,000, positive Wassermann	Purulent meningitis	Good
Authors'	M	6	Typhoid	Rigid, involuntaries Improved Otitis, involuntaries	7th 11th 21st	23d	22d day, spinal fluid turbid, increase in cells, lymphocytes culture, pure typhoid, postmortem same two strains of typhoid B1 agglutinated 1:6,000, B2 agglutinated 1:24,000	Purulent meningitis, more anteriorly typhoid spleen slight intestinal lesions	Good

cases where such contamination during spinal puncture may have occurred

Lyall<sup>4</sup> regarded Neuman and Schaeffer's<sup>5</sup> case as being one of true purulent typhoid meningitis. Of course, the now known laboratory tests were not applied, but it appears that their tests were conclusive, since only the potato culture was questionable. In Lyall's own case, the culture showed an atypical typhoid, in that only after several generations was it motile, and then only slightly. Then, only, was it agglutinated by known typhoid serums, but best by an homologous serum which agglutinated also known typhoid bacteria.

O'Carroll and Purser<sup>6</sup> noted Osler's eleven cases of central nervous system lesions in two thousand cases of typhoid, and Curschman's five in his own experience, but, unfortunately, bacteriologic examinations were not complete. O'Carroll found fifteen reported cases where typhoid bacilli alone caused a meningitis, and estimated that there are not more than thirty cases in all. They believed that the purulent condition of the brain is only an advanced stage of an edema often described—with which we, of course, agree.

D'Oelsnitz<sup>7</sup> and Amenille<sup>8</sup> described cases with increased cell count in the spinal fluid, but no turbidity nor increased pressure, and the latter briefly described another case which cleared up for them after the postmortem examination.

An astonishing finding to us, and one already noted by others (Fernet<sup>9</sup>) is the frequent lack of the usual typhoid lesions, although many of the cases showed positive Widal and blood cultures. In six cases here recorded, special mention was made that little or no intestinal lesions were present, in some, the spleen was quite normal. In our case, there was no evidence of intestinal lesion, except one inch above the ileocecal valve. The mesenteric glands and spleen were markedly enlarged. In our case, too, the marked dilatation of ureters and urinary tubules with no apparent cause was noted. Of course, we must admit that the intestinal lesions may have healed. Against this theory in many cases, is the relatively short course of the disease.

4 Lyall, H. W. Meningitis in an Infant Caused by the Typhoid Bacillus, *J. Med. Res.* **22** 457, 1912.

5 Neuman, H. and Schaeffer, R. Zur Aetiologie der eitrigen Meningitis, *Virch. Arch.* **109** 477, 1887.

6 O'Carroll, J., and Purser, F. C. On a Case of Meningitis Due to Bacillus Typhosus, *Tr. Roy. Soc. Med. Ireland* **30** 108, 1912.

7 d'Oelsnitz, M., Bourcart, G., and Ronchese, M. A. Un cas de meningite cerebro spinale eberthienne, *Bull. et mem. Soc. med. d. hop. de Par.* **39** 276, 1915.

8 Ortoconni, A., and Amenille, P. Accidents meninges precoces dans la fièvre typhoïde, *Bull. et mem. Soc. med. d. hop. de Par.* **31** 187.

9 Fernet, Ch. Meningite typhoïde par bacille d'Eberth, *Bull. et mem. Soc. med. d. hop. de Par.*, 1891, p. 361.

In several cases were noted—and this is particularly true in Bonnamour and Macrygenis<sup>10</sup> and our cases—that the anterior portion of the brain showed a more marked purulent condition than the posterior. This is evident even in the photograph, but was especially noted at the postmortem table. However, a collection of pus below the cere-

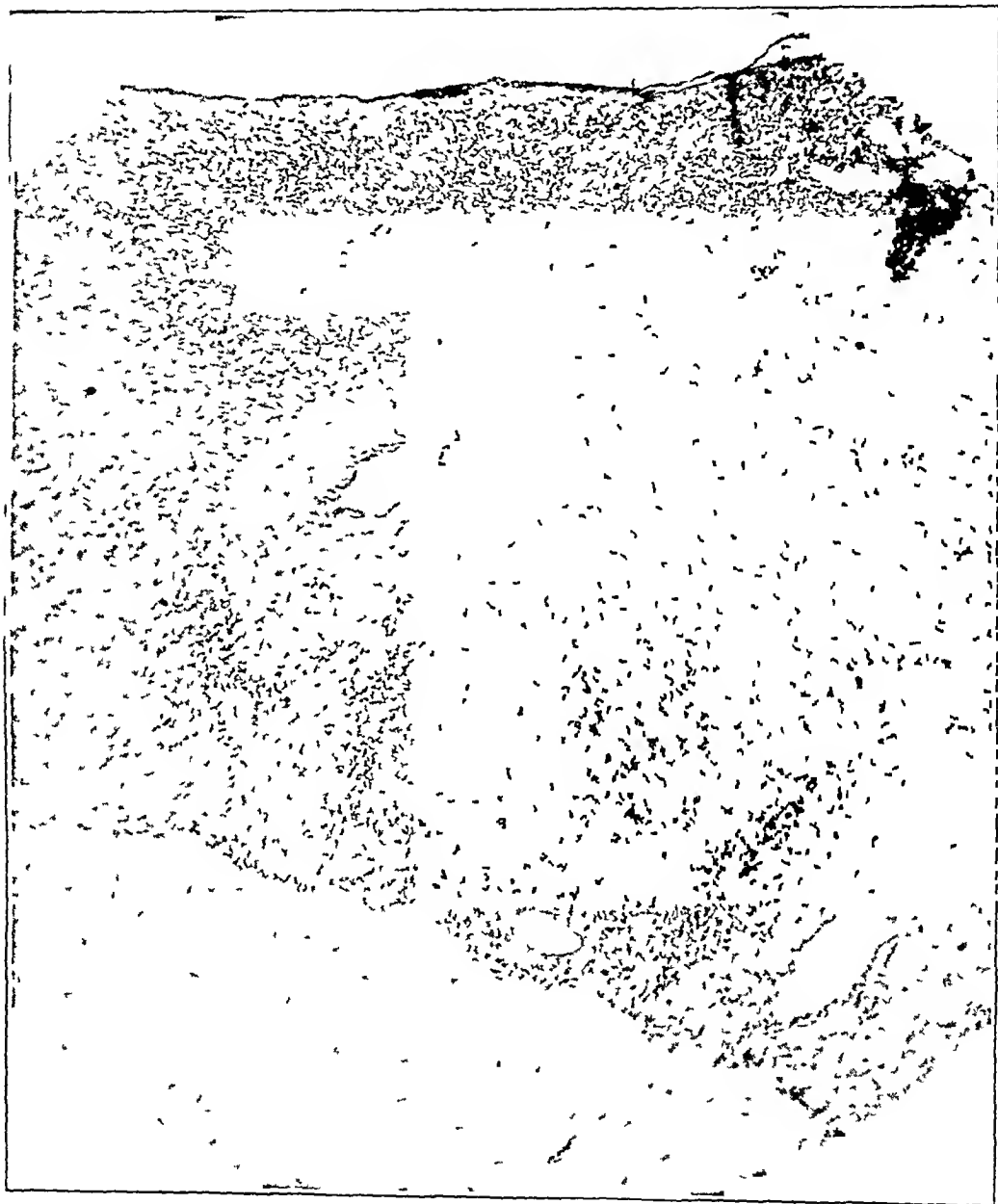


Fig 3—Photograph of a 10 micron section of the meninges over the frontal lobe (ocular, 4, objective, 3 [Leitz])

bellum was also noted. The ventricles in our case, differing from others, were not enlarged, but contained a turbid fluid on examination.

10 Bonnamour, S, and Macrygenis, A. Meningite aiguë purulente eberthienne au cours d'un fièvre typhoïde. Presence du bacille d'Eberth dans le liquide céphalo-rachidien, *Lyon med* 126 397, 1917.

Lesieur and Marchand<sup>11</sup> were able to find only nine cases in the literature in which the typhoid bacillus had been grown from the spinal fluid before death. Fifteen of the cases reported herein specifically state that the typhoid organism was isolated during life from the spinal fluid. Cole's<sup>1</sup> table does not state whether culture was made before or after death. In some, apparently, they were made at the postmortem, in one, on the day of death, in others, the time is not quite clear. However, we have reviewed other cases, not here tabulated, in which the typhoid bacillus was obtained from the spinal fluid where no purulent condition supervened, and where death did not follow. These probably belong to Cole's serous meningitis cases. Cole, in thirteen cases of serous meningitis, shows that in six the typhoid bacillus was grown from the spinal fluid in pure culture during life, and that it was grown from the others after death. Therefore, quite occasionally, the typhoid bacilli may be grown, although there is no change in the gross appearance of the spinal fluid.

In only six cases did Lemierre and Joltrain<sup>12</sup> find a primary typhoid meningitis — or rather, one apparently not following intestinal typhoid — as their case showed an otitis media very early, although, as they stated, the meningitis may not have been secondary to the otitis. Apparently, two other cases in our table were either primary or secondary to a typhoid other than intestinal — one of them to an infraorbital war wound. In several of the cases occurring in soldiers, no clear history was obtainable. These may have had a primary abdominal infection.

Lemierre and Joltrain also point out the peculiarity in meningitis cases of the spinal fluid agglutinating the organism. They believe that this is exceptional, as it has been stated that agglutinins, although present in blood, have not been observed in the spinal fluid. In their case, the spinal fluid agglutinated the organism grown from it, and also laboratory strains. Bayne-Jones<sup>2</sup> states that in serous cases, the spinal fluid contains agglutinins for *B. typhosus*.

Several investigators found a clear fluid in early lumbar punctures, and later, turbidity and increased pressure. In only very few was a definite cell count reported. O'Carroll and Purser<sup>6</sup> and Lemierre and Joltrain<sup>12</sup> reported relatively high polymorphonuclear leukocytes in their earlier counts, although in the latter, a later count showed an increase of small round cells. Bonnamour and Macrygenis<sup>10</sup> reported

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11 Lesieur, C., and Marchand, M. J. Etat meningé au cours d'un fièvre typhoïde. Evolution bénigne après la ponction lombaire, Bull. et mem. Soc. med. d'hop. de Par. **34** 785, 1912, Ibid., 780.

12 Lemierre, A., and Joltrain, E. Meningite purulente Eberthienne début par symptômes d'otite aiguë, Bull. et mem. Soc. med. d'hop. de Par. **34** 581 1912.

in their first count a predominance of lymphocytes and in a later count 80 per cent polymorphonuclears. Unfortunately, no differential count was made in either of our counts, but there was noted a predominance of mononuclears.

MacCallum<sup>13</sup> carefully described the minute pathology of typhoid meningitis. Others<sup>14</sup> have found in general the same results as MacCallum. Our sections do not show the congestion of the veins, nor the blocking of the arteries by a cellular infiltration of the vessel wall and an endarteritis, as MacCallum appears to have found. In fact, we see in our sections that the cellular infiltration is less marked about the blood vessels than elsewhere, especially about the veins. It is possible that we are dealing with a more recent meningeal involvement than MacCallum had, for Cole noted that in that case meningeal symptoms were marked for one week before death with the bacilli already in the spinal fluid.

In our table, which includes twenty-three cases, the ages of the patients vary from 4 months to 55 years. There are eighteen males and five females. Cole's patients varied in age from 4 to 46 years, with five males and three females, three under 20 years, two over 40. Our table shows nine patients under 20 and three over 40 years of age.

Symptoms of meningeal irritation are so frequent in typhoid cases that it is difficult to judge when the real meningitis begins. If daily spinal punctures are made, of course, the date of a turbid fluid might be an index. So far, we know of no definite symptom that can be taken as an index of a purulent meningitis. In our case, were an early restlessness, involuntary voiding of urine and feces, and rigidity an index of purulent meningitis? Of meningeal irritation, of course! Or was this the second stage, after the gallbladder involvement, with otitis, involuntary voiding of urine and feces and convulsions? We have taken the latter view. And so, in other cases, we have taken what seemed to be the final meningeal flare-up before death as the stage of onset of purulent meningitis. Judging thus, we find its onset varies

13 MacCallum, W. G. The Pathological Anatomy of Meningitis Due to *Bacillus Typhosus*, Johns Hopkins Hosp. Rept. **12** 411, 1904.

14 Cintra, U. Meningite purulenta com bacillo de Eberth isolado do liquido cephalo-rachiano, Ann. Paulistas de med. e Cir. **9** 64, 1918. Crouchet and Buaid. Sur un cas de meningite cerebro-spinale typhique, avec presence du bacille d'Eberth dans le liquide cephalo-rachidien, Gaz. hebdomadaire de med. de Bordeaux, 1902. Dehille. Pediatr. prat. Lille **3** 89, 1905. Lavenson, R. S. Univ. Penn. Med. Bull. **21** 55, 1902. Merklen and Gautier. Meningite aigue eberthienne a forme purulente. Presence du bacille typhique dans le liquide cephalo-rachidien, Presse med., Jan. 22, 1917, p. 51. Milligan, E. H. M. Isolation of the Typhoid Bacillus from the Spinal Fluid from a Case of Typhoid with Cerebrospinal Symptoms, Brit. M. J. **1** 1295, 1908. Nietter, A. Ueber den Nachweis vom Typhusbacillen der Cerebrospinalflüssigkeit bei typhus abdominalis, München med. Wchnschr. **55** 1009, 1908.

from the first to the thirty-fifth day Symptoms lasted then, for from one to ten days, some showing convulsions, but many with other meningeal symptoms of involuntary sphincteric relaxation, vomiting, intense headache, contraction of various muscles, frequently of the hands and face Cole found that symptoms began late from the second to the fifth week, and lasted for from two to five days



Fig 4—Photograph of the meninges near a blood vessel showing perivascular infiltration and the denser infiltration away from the blood vessels (ocular, 4 objective 6)

We have not accepted two of the cases put in Bayne-Jones report, one by Gurd and Nelles<sup>15</sup> which seems to have been an abscess above the dura following an injury and not a meningitis, even though

15 Gurd F B and Nelles T B Intracranial Abscess Due to the Typhoid Bacillus *Ann Surg* 47 4, 1908 Henry, J N and Rosenberger I C R Purulent Cerebro-spinal Meningitis Caused by the Typhoid Bacillus without the Usual Intestinal Lesions of Typhoid Fever *Am J M Sc* 135 240 1908

typhoid bacilli were isolated. The other (Raymond and Siccard<sup>16</sup>) was an infection localized in the lumbar region, from which pus and a pure culture of typhoid was obtained. After laminectomy, the patient recovered. To us it seems that purely localized typhoid infection of the meninges, especially with recovery, should not be included.

The prognosis, as shown by our table, is very bad. Excepting the two cases, quoted above, neither of which is included in our table, there have been no recoveries. It is to be remembered, that in thirteen cases of serous meningitis Cole found only one recovery. Although Bayne-Jones does not give the number of recoveries from serous meningitis in his table, he quoted Claret and Lyon-Caen as having found eight recoveries in thirteen cases. Cole showed that there were no recoveries in his fourteen cases of purulent meningitis.

The question of treatment may seem out of place in a disease which has been so uniformly fatal. Possibly prophylaxis offers the best hope. Lenneire and Joltian,<sup>12</sup> after removal of spinal fluid, introduced electricity, evidently with no results. But since some recoveries occur in some serous cases, and some have noted a marked improvement following lumbar puncture, repeated punctures may help. Even in some cases with amelioration of symptoms after puncture, which usually showed clear fluid, a purulent fluid formed later and death supervened.

To us, it seems that a purulent spinal fluid, with cultures showing typhoid bacilli, is proof enough of a typhoid meningitis. Of course, this does not mean that necropsies should not be obtained, nor that other organisms may not be responsible. But even in mixed infections, except for statistical reports, what does it matter if other organisms are present?

Purulent typhoid meningitis has been noted usually following abdominal typhoid, but also as secondary to other typhoid as witness one otitic and one infraorbital wound.

Cole reported fourteen cases and Bayne-Jones eighteen. We have ruled out two of the latter and added seven more. All gave pure typhoid cultures from the spinal fluid, most of them before death. In all these cases the organism has been isolated with a fair degree of accuracy. All cases noted have terminated fatally.

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<sup>16</sup> Raymond, F, and Siccard, J. A. Epidurite purulente lombaire a bacilles d'Eberth dans la convalescence d'une fièvre typhoïde. Paraplégie. Ponction lombaire, Bull et mem Soc méd d hôp de Par **22** 860, 1905. Robinson, J. E. Case of Primary Typhoid Meningitis. South M J **8** 37, 1915. Southard, E. E., and Richards, E. T. F. Typhoid Meningitis, J Med Res **19** 513, 1908. Staubli, C. Meningismus typhosus und Meningotyphus, Deutsch Arch f klin Med **82** 90 1905. Symmers and Wilson. J Path & Bacteriol **13** 251, 1909 (quoted from Bayne-Jones). Stuhmer, A. Typhusbazillen in der Zerebrospinalflüssigkeit. München med Wchnschr, 1911, p 357.



# OBSERVATIONS ON CHANGES IN FORM OF THE INITIAL VENTRICULAR COMPLEX IN ISOLATED DERIVATIONS OF THE HUMAN ELECTRO-CARDIOGRAM

F A WILLIUS, M D

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The literature of recent years has contained numerous contributions dealing with abnormalities of the initial ventricular complex Q R S of the electrocardiogram. Most authors,<sup>1</sup> however, have dealt largely with changes affecting all derivations consisting of abnormalities in complex contour or increase in the complex base width exceeding the recognized normal -

Differences of opinion exist as to the cardiac disorder responsible for these deviations from the normal. Most observers, I believe recognize myocardial changes affecting the ventricular conduction system, locally or diffusely. Robinson<sup>3</sup> takes issue with the majority, and emphasizes the role of functional myocardial fatigue. He presents electrocardiograms of a patient in which the aberrant complexes approach normal, yet do not attain normal after digitalis and rest. I have not had the opportunity of observing the abnormal complexes return to normal when all three derivations have been affected. In a previous article<sup>4</sup> I called attention to the high mortality attending this disorder, and emphasized the progression of the disease. The obvious criticism of this article is the paucity of necropsy material and the incomplete histologic data. Careful serial histologic examinations have been in progress for some time and will be reported later.

The fact that these patients rapidly show myocardial disintegration and die seems to me to indicate structural changes in the majority of instances at least, even in the absence of conclusive pathologic data

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1 Carter, E P. Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations, *Arch Int Med* **22** 331 (Sept) 1918

Oppenheimer, B S and Rothschild, M A. Electrocardiographic Changes Associated with Myocardial Involvement. *I A M A* **69** 429 (Aug 11) 1917

Robinson, G C. The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *Arch Int Med* **18** 830 (Dec) 1916

2 Lewis, T. *Clinical Electrocardiography*, London Shaw, 1913, p 120

3 Robinson, G C. The Significance of Abnormalities in the Form of the Electrocardiogram. *Arch Int Med* **24** 422 (Oct) 1919

4 Willius, F A. Arborization Block. *Arch Int Med* **23** 431 (April) 1919

The frequency of abnormalities of the QRS complex in isolated derivations of the electrocardiograms prompted this study to determine, if possible, the clinical significance of these findings. Wedd<sup>5</sup> published thirty such cases, in twenty-one of which a definite clinical diagnosis of heart disease was made, and in nineteen of which myocardial disease was noted. Three cases were diagnosed syphilis and one case was diagnosed chronic nephritis without reference to the cardiovascular system. In five cases no clinical diagnoses were

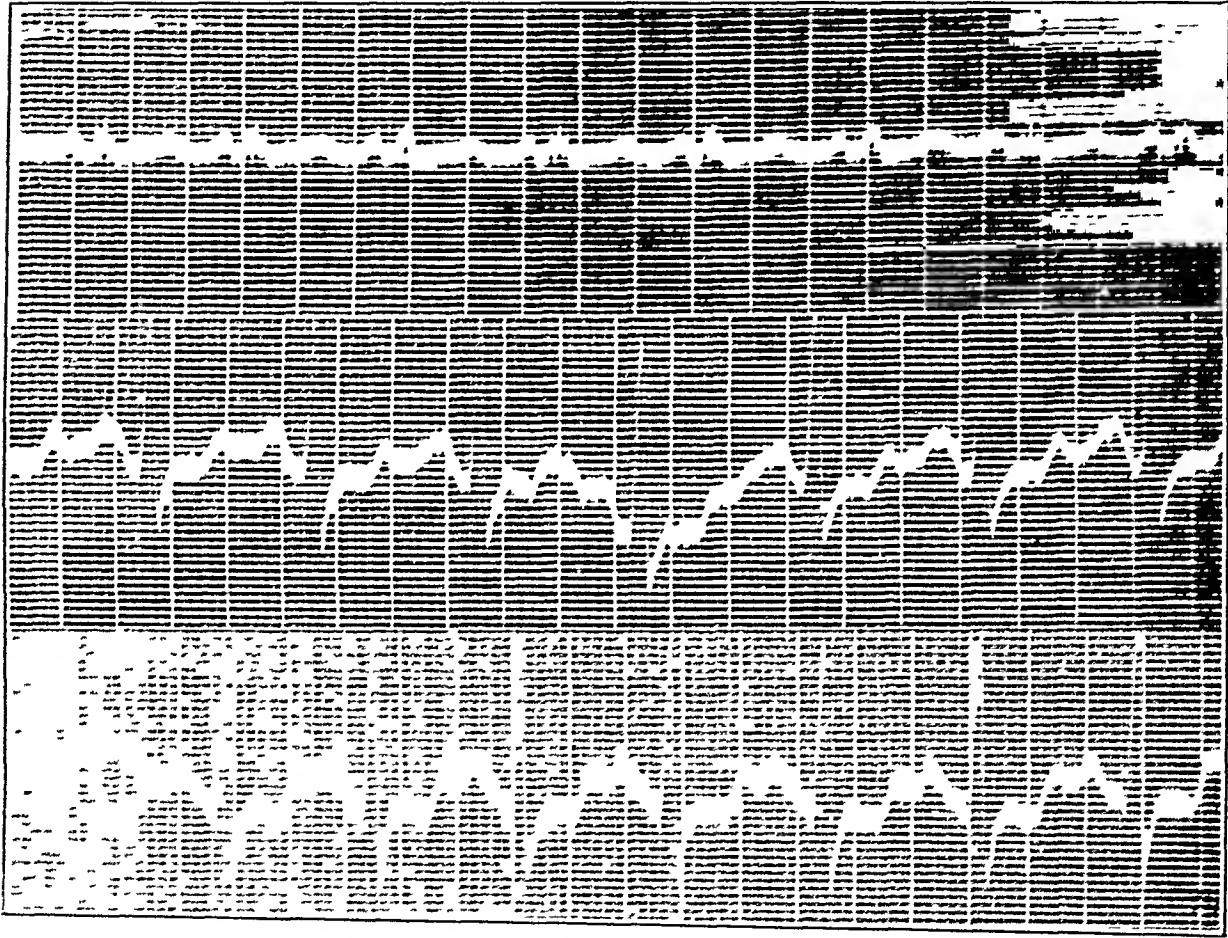


Fig 1 (Case 172,578) —Notched QRS, Derivation 1

recorded. In conclusion, Wedd states 'Slight notching or localized thickening of the R complex of the electrocardiogram is frequently encountered in cases of unquestioned myocarditis. While no quantitative value can be assigned to such notching, it is believed, when permanent, to indicate pathologic changes in the myocardium, and when transient to reveal a temporary or potential defect in the conduction system.'

<sup>5</sup> Wedd A M. The Clinical Significance of Slight Notching of the R-wave of the Electrocardiogram, *Arch Int Med* 23:515 (April) 1919.

This study comprises 747 cases and covers a period of five and one-half years. The cases were divided into two major groups, cases (550) with QRS complexes definitely notched, and cases (197) with slurring or localized thickening of the ascending or descending limb, or both. Both groups were subdivided according to derivation occurrence. The accompanying electrocardiograms illustrate the abnormalities under discussion (Figs 1-6).

*Notched QRS Complexes*—Seventy-seven cases (14 per cent) were placed in Derivation 1, eighty-three (15.1 per cent) in Deriva-

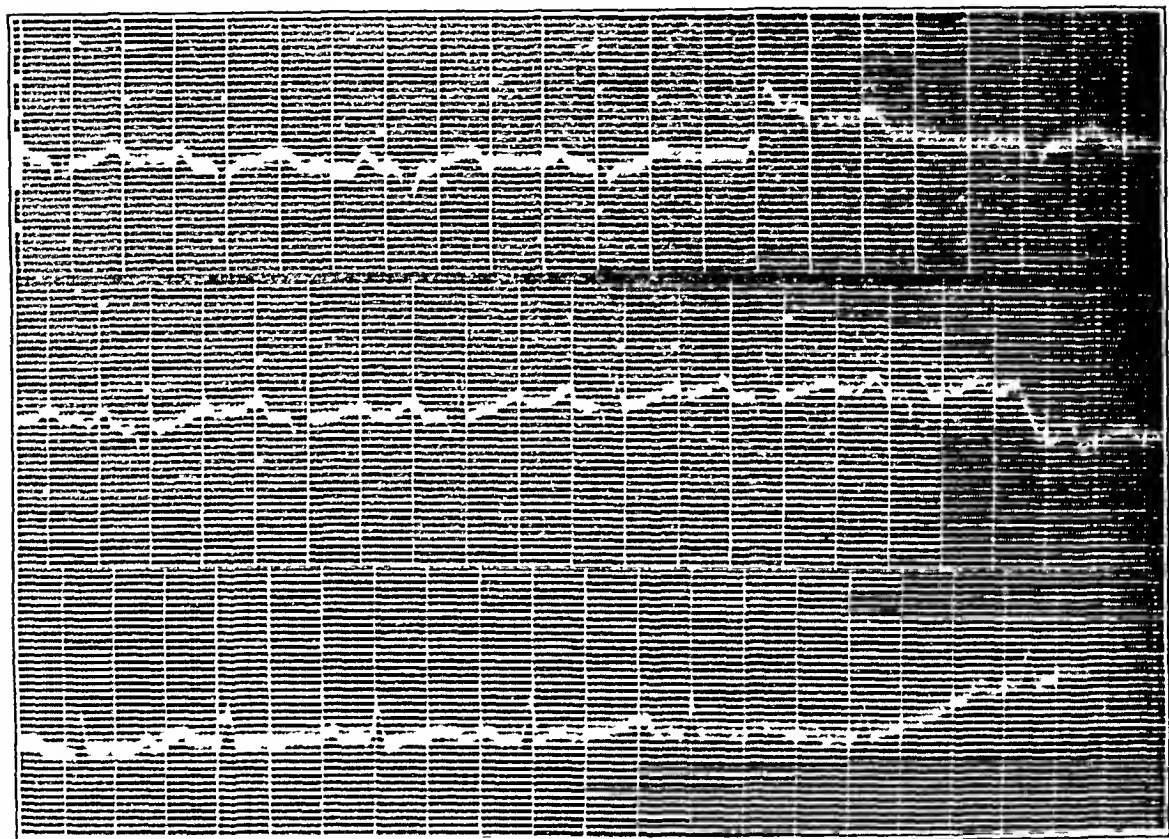


Fig 2 (Case 293,424) —Notched QRS, Derivation 2

tion 2, and the greatest number, 390 (70.9 per cent) in Derivation 3. In more than one half (53.1 per cent) of the cases, the electrocardiograms were associated with preponderance of the left ventricle. Table 1 illustrates this occurrence. This relationship at once directs attention to the left ventricle as the possible seat of disturbance at least in the majority of cases.

Etiologic disorders occurring in this group in order of frequency were (1) degenerative processes, (2) infections, (3) local nutritional disturbances, and (4) congenital heart disease. These findings are summarized in Table 2.

There was definite evidence of heart disease in all except eighty-one cases (14·7 per cent). This group was clearly separated in order to avoid confusion in the final analysis, but it is recorded because the electrocardiographic findings were clear cut. The elapse of more time may throw light on this extremely interesting group.

Negativity of the final ventricular T wave occurred in almost half the cases (41·8 per cent), and was most frequently observed in Derivation 3 (66·4 per cent). There was no instance of T wave negativity in Derivation 2, or in Derivations 1 and 3 in combination. This summary is found in Table 3.

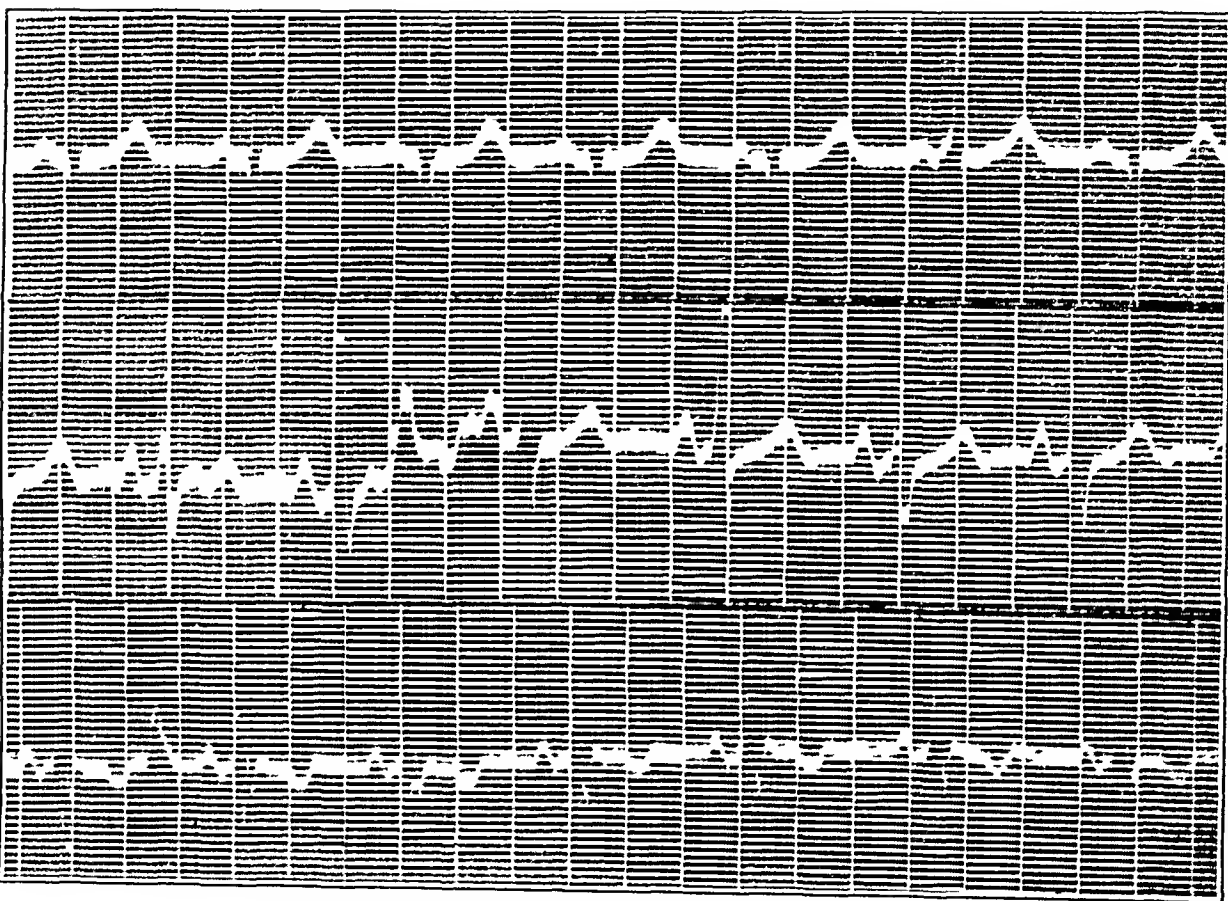


Fig. 3 (Case 297,104) —Notched QRS, Derivation 3

Auricular fibrillation occurred in seventy-six cases (13·8 per cent), this infrequency seems to indicate that these patients as a group are still possessed with relatively efficient myocardiums. Delay in auriculo-ventricular conduction occurred in only six cases.

Information has been received concerning 410 patients, ninety-seven (23·7 per cent) of these have died from heart disease. The highest mortality occurred in Derivation 2 (37 per cent). A control series corresponding in number, sex and occurrence by decade, and excluding the graver types of heart disease, such as angina pectoris, aneurysm, arborization block, disease of the auriculoventricular bundle



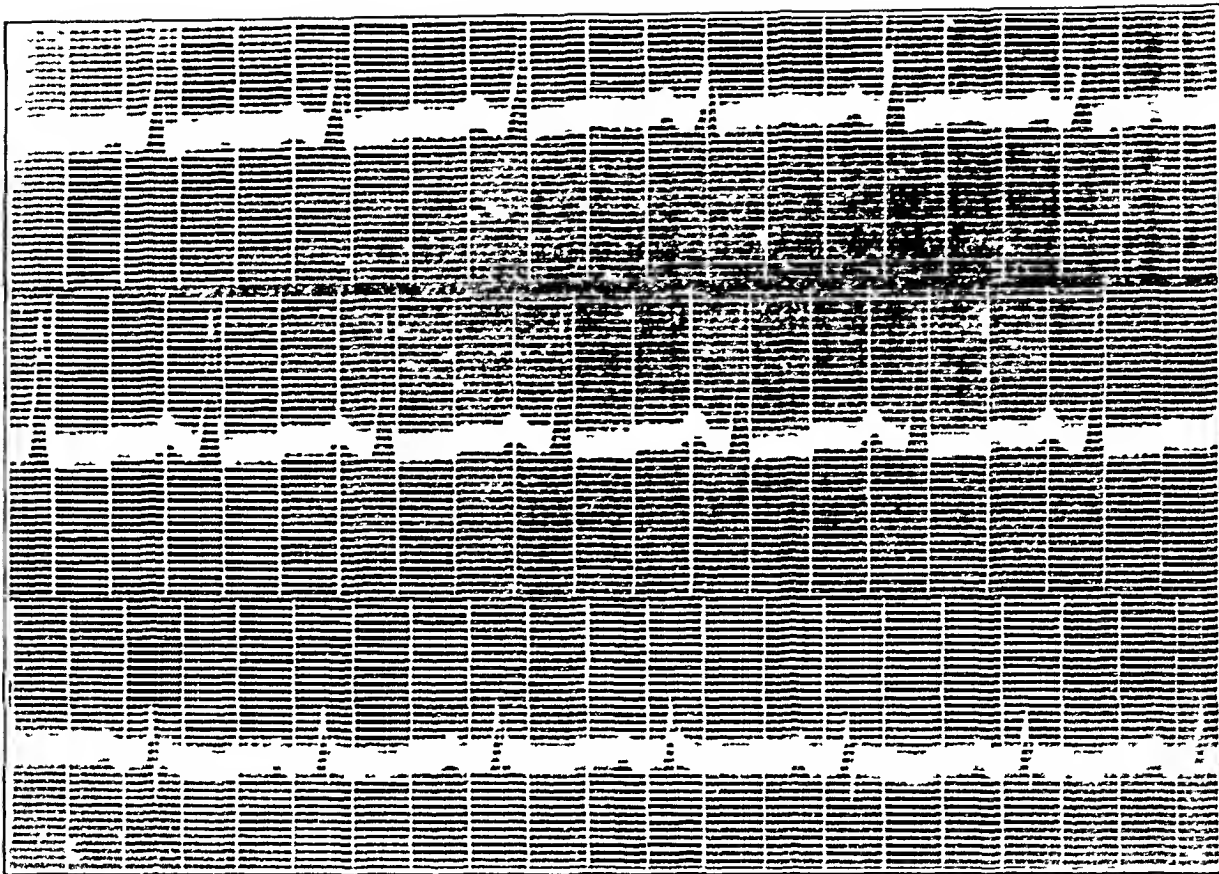


Fig 4 (Case 287,083) —Slurred QRS, Derivation 1

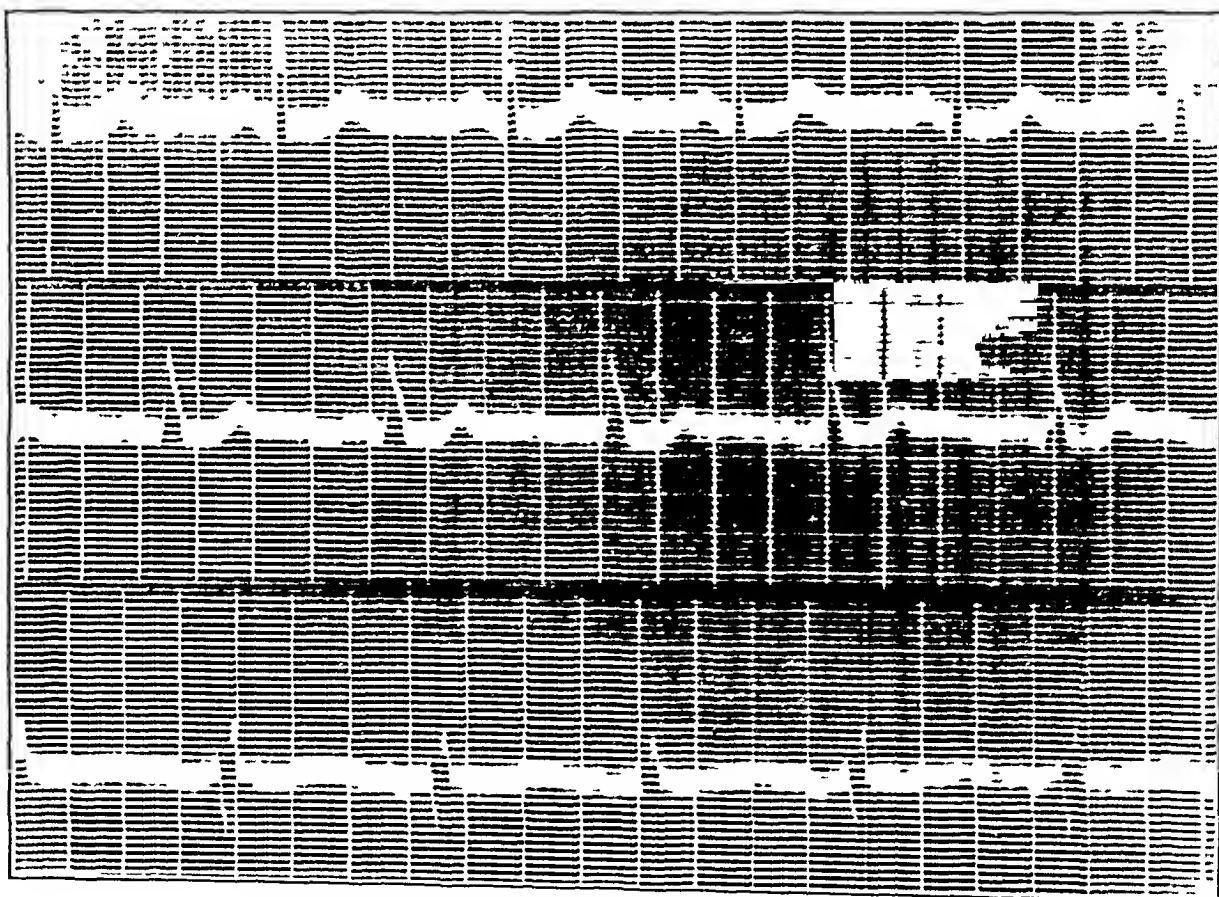


Fig 5 (Case 271,992) —Slurred QRS, Derivation 2

TABLE 4—MORTALITY IN NOTCHED COMPLEXES DERIVATION 1

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
1 10	4	3	1	2	1		2	0	2	0	0
11 20	8	4	0	4	3		1	1	0	0	0
21 30	23	11	5	6	0		11	4	5	2	0
31 40	12	9	3	6	4	* \ Pneumonia y Influenza z Abdominal hemorrhage	5	4	1	0	1
41 50	11	8	2	6	4		4	2	0	2	0
51 60	13	10	4	6	4		6	2	2	1	0
61 70	5	4	3	1	2	\ Cancer of the rectum	2	2	0	0	0
71 80	1	1	1	0	0		1	1	0	0	0
Total	77	50	19	31	18		32	16	11	5	1

14 cardiac deaths, 28 per cent

\* Each letter refers to a single death other than cardiac

TABLE 5—MORTALITY IN NOTCHED COMPLEXES, DERIVATION 2

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
1 10	1	1	1	0	0		1	0	0	1	0
11 20	1	0	0	0	0		0	0	0	0	0
21 30	6	3	1	2	1		2	0	0	2	0
31 40	10	6	1	5	3	\ Pneumonia	4	1	1	1	0
41 50	18	11	6	5	3		8	3	5	0	0
51 60	26	16	12	6	6		10	2	6	2	0
61 70	19	13	11	2	3		6	2	3	2	0
71 80	2	2	2	0	2		0	0	0	0	0
Total	83	54	34	20	21		33	8	16	9	2

20 cardiac deaths 37 per cent

TABLE 6—MORTALITY IN NOTCHED COMPLEXES, DERIVATION 3

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
1 10	4	2	1	1	0		2	0	1	1	1
11 20	19	14	4	10	3		11	1	6	2	5
21 30	62	50	19	31	8		42	10	23	9	7
31 40	82	61	24	37	8	\ Diabetes y Influenza z Nephritis	53	19	24	10	10
41 50	99	80	29	51	18	y Cancer	62	23	22	17	10
51 60	76	59	37	22	21	w Cancer y Cancer of the pancreas z Pneumonia	38	9	18	11	1
61 70	41	36	25	11	13	\ Pneumonia y Tuberculosis	23	8	7	8	2
71 80	7	4	4	0	3	z	1	0	1	0	0
Total	390	306	143	163	74		232	70	104	58	36

63 cardiac deaths 20.6 per cent



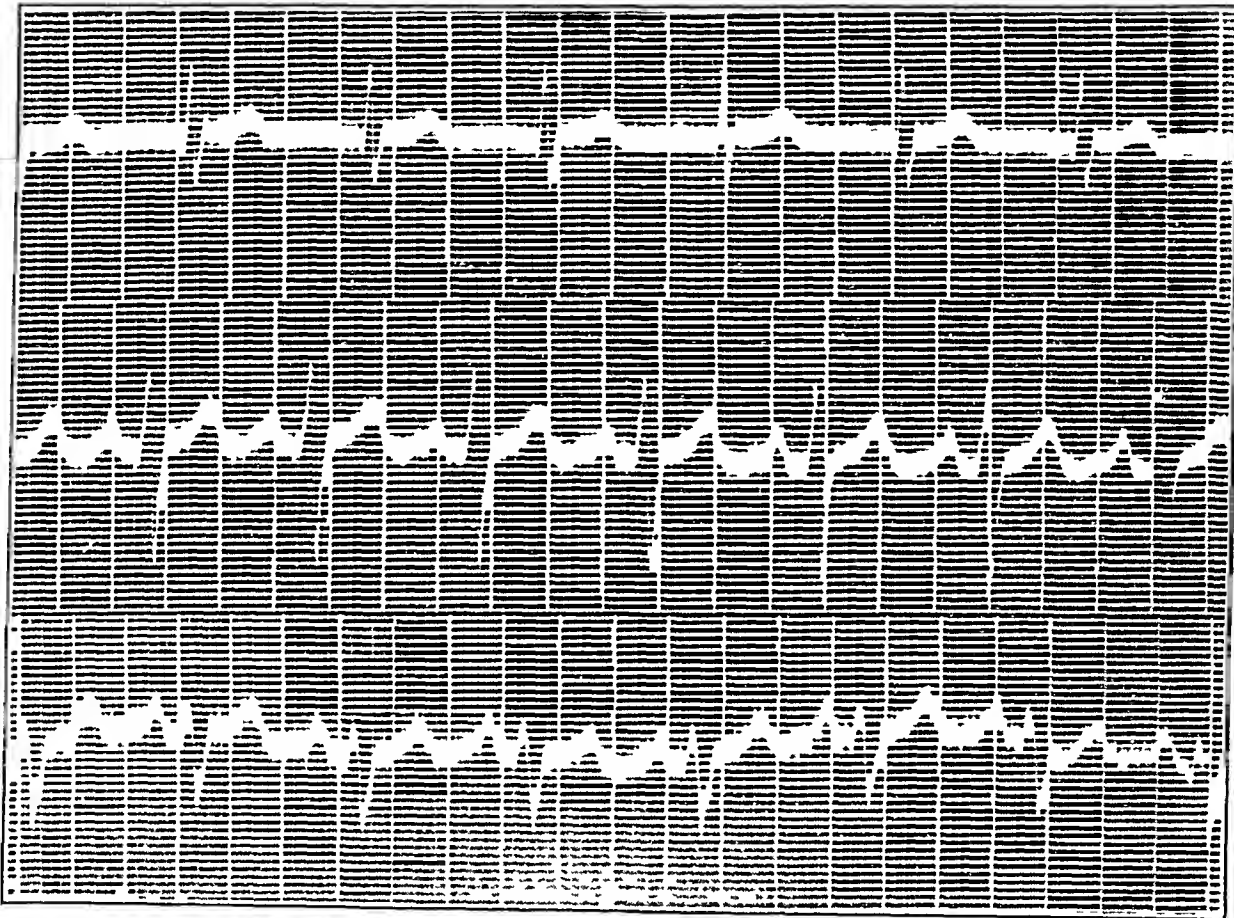


Fig 6 (Case 293,897) —Slurred Q R S, Derivation 3

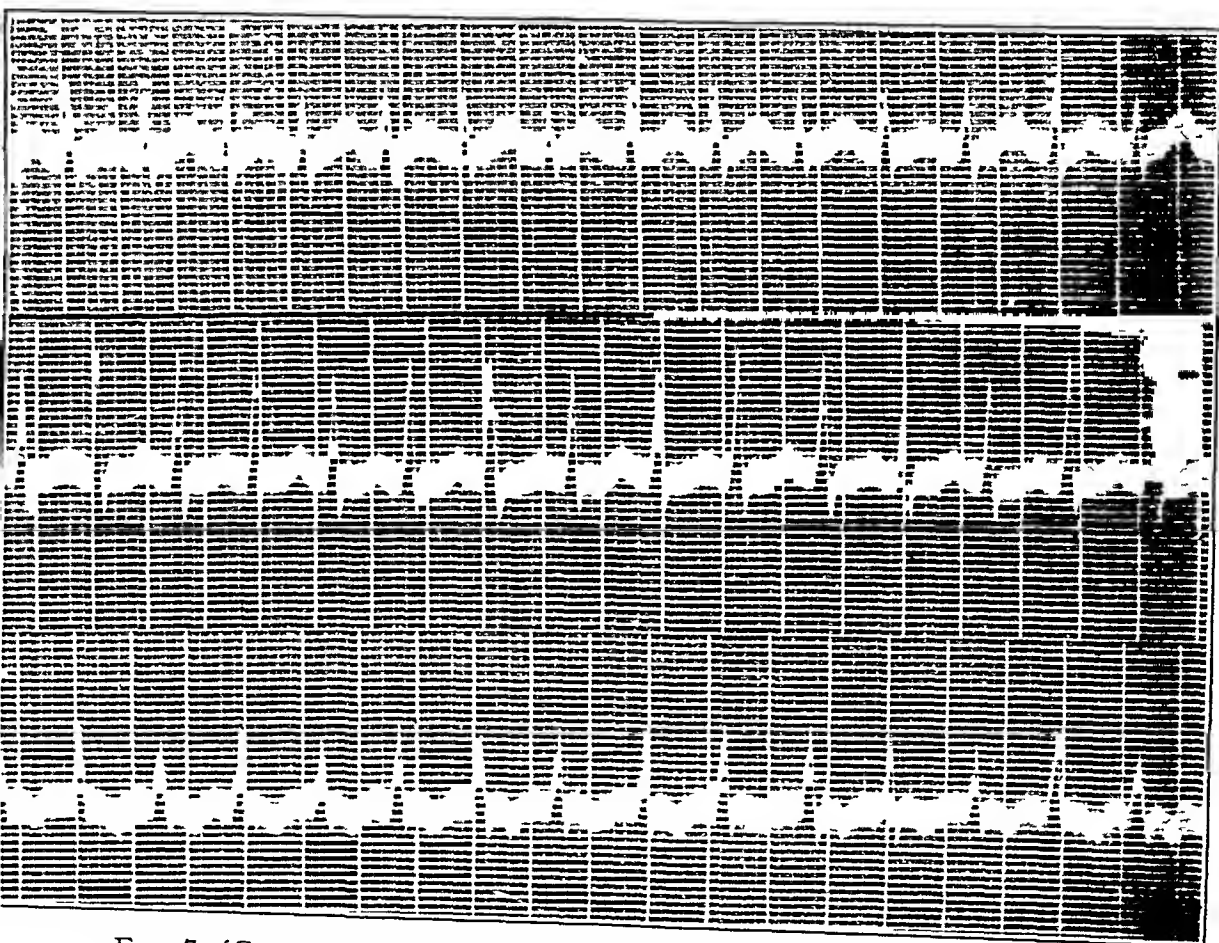


Fig 7 (Case 252 579) —Slurred Q R S, Derivation 3 Negative T wave,  
Derivation 3 Nodal tachycardia Feb 28 1919



TABLE 7—TOTAL MORTALITY IN NOTCHED COMPLEXES

	Total	Patients Heard From	Males	Females	Cardiac Deaths	Mortality percentage	Living	Worse	Improved	Unchanged	No cardiac Symptoms
Derivation 1	77	50	19	31	14	28.0	32	16	11	5	1
Derivation 2	83	54	34	20	20	37.0	33	8	16	9	2
Derivation 3	390	306	143	163	63	20.6	232	70	104	58	36
Total	550	410	196	214	97	23.7	297	94	131	72	39

TABLE 8—CONTROL SERIES

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged
1-10	9	6	3	3	1		5	2	1	2
11-20	28	17	7	10	3	1 Thyroidectomy (exophthalmos)	14	4	6	4
					1	Hyperthyroidism				
21-30	91	63	23	40	5	1 Influenza	58	14	27	17
					1	Hyperthyroidism				
31-40	104	78	32	46	11	1 Pneumonia	67	13	22	32
					1	Pneumonia				
					1	Pneumonia				
41-50	128	96	48	48	11	2 Nephritis	85	35	34	16
					1	Pneumonia				
					1	Cancer				
					1	Cerebral hemorrhage				
51-60	115	90	37	33	24	2 Cancer of stomach	66	30	22	14
					1	Cancer of stomach				
					1	Pneumonia				
					1	Cancer				
					1	Peritonitis				
61-70	65	47	36	11	18	2 Pneumonia	29	13	6	10
					1	Cancer of tongue				
					1	Cancer of rectum				
					1	Cancer				
					1	Cancer				
71-80	10	7	6	1	3	2 Apoplexy	4	1	0	3
					1	Pneumonia				
Total	550	404	212	192	76		328	112	118	98

48 cardiac deaths 11.8 per cent

TABLE 9—MORTALITY IN TWAVE NEGATIVE NOTCHED COMPLEXES

T Wave Negativity	Total	Patients Heard From	Males	Females	Cardiac Deaths	Mortality percentage	Living	Worse	Improved	Unchanged	No cardiac Complaints
Derivation 1	34	28	23	5	15	52.6	11	1	8	2	0
Derivation 2	0	0	0	0	0	0.0	0	0	0	0	0
Derivation 3	174	103	33	70	14	13.6	86	31	34	21	10
Derivations 1 and 2	11	10	4	6	6	60.0	4	1	3	0	0
Derivations 2 and 3	25	17	9	8	4	23.5	10	2	6	2	1
Derivations 1 and 3	0	0	0	0	0	0.0	0	0	0	0	0
Derivations 1, 2 and 3	8	4	2	2	2	55.0	0	0	0	0	0
Total	232	162	71	91	42	25.0	111	35	51	25	11

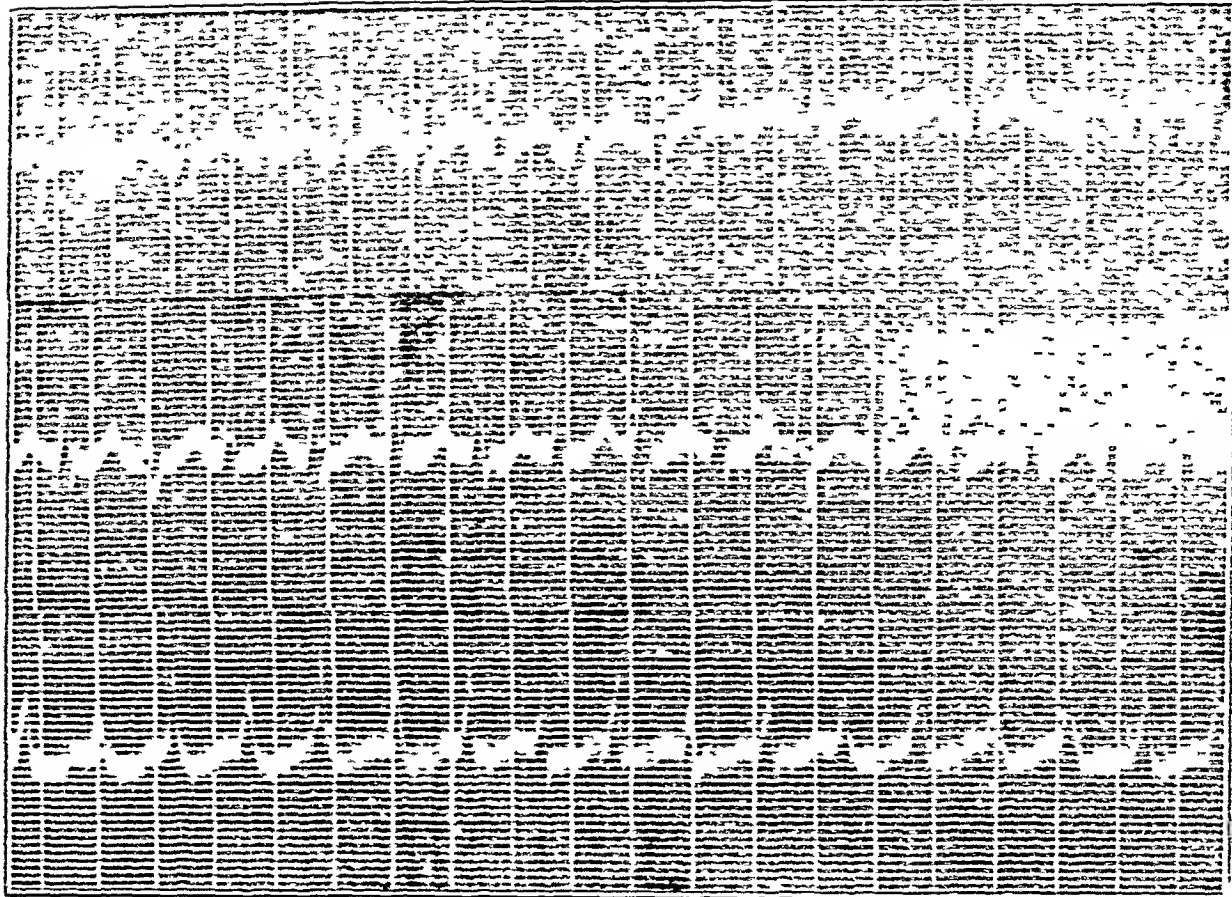


Fig 8 (Case 252579) —Notched QRS Derivation 3 showing progression  
 Aug 15, 1919

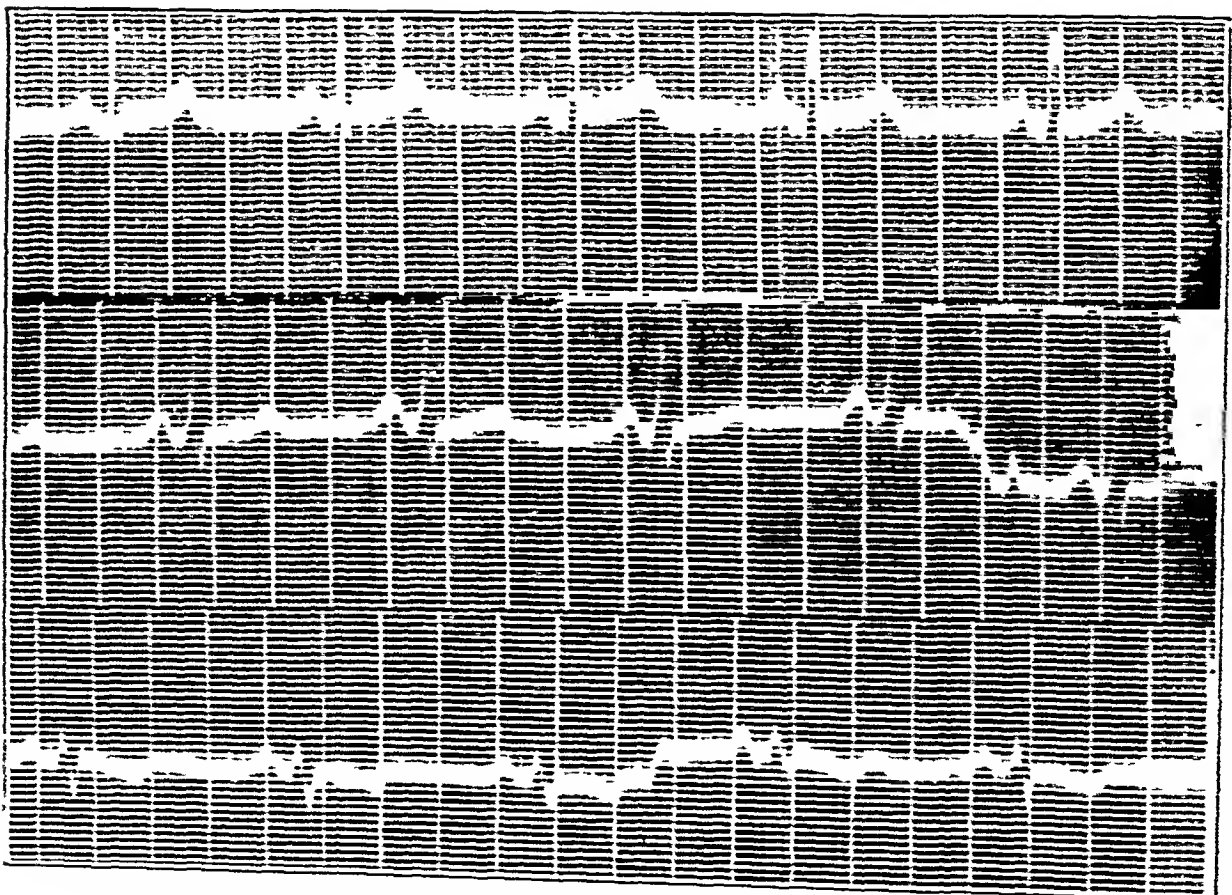


Fig 9 (Case 252579) —Notched QRS Derivation 3 Sinus rhythm. Aug  
 18 1919 just after tachycardia subsided

TABLE 10—VENTRICULAR PREPONDERANCE IN SLURRED COMPLEXES

Deende	Derivation 1			Derivation 2			Derivation 3		
	Left Preponderance	Right Preponderance	No Preponderance	Left Preponderance	Right Preponderance	No Preponderance	Left Preponderance	Right Preponderance	No Preponderance
1-10	0	1	1	0	0	0	0	0	0
11-20	0	4	1	0	0	0	2	0	0
21-30	2	10	6	2	0	0	3	5	2
31-40	3	6	8	2	2	1	12	5	15
41-50	6	6	4	4	0	6	6	1	6
51-60	5	1	0	9	0	1	16	1	9
61-70	1	1	1	6	0	2	6	1	4
71-80	0	0	0	1	0	0	0	0	0
Total	17	29	21	24	2	10	45	13	36

TABLE 11—ETIOLOGIC CONDITIONS IN SLURRED COMPLEXES

	Total	Degenerative Processes			Infections			Nutritional Disturbances			
		Hypertension With and Without Clinical Nephritis	Exophthalmic Goiter	Adenomas With Hyperthyroidism	Endocardial Valvular Disease	Chronic Myocarditis	Syphilis	Arteriosclerosis	Angina Pectoris (Patients with arteriosclerosis)	Congenital Heart Disease	Inconclusive Clinical Cardiac Findings
Derivation 1	67	5	9	2	28	6	2	4	3	1	10
Derivation 2	36	8	3	2	6	5	1	5	4	0	5
Derivation 3	94	22	13	2	10	8	4	7	3	1	27
Total	197	35	25	4	44	19	7	16	10	2	42
Percentage		17.8	12.7	2.0	22.3	9.6	3.5	8.1		1.0	21.3
		34.0			35.4						

TABLE 12—T WAVE NEGATIVITY IN SLURRED COMPLEXES

[illegible]

and auricular flutter, revealed a cardiac mortality of 11·8 per cent. This difference in mortality is certainly definite.

Two hundred ninety-seven patients are alive, ninety-four report their conditions as being worse, 131 as improved, and seventy-two as unchanged. Thirty-nine report no cardiac complaints. Tables 4 to 8 summarize these findings.

TABLE 13—MORTALITY IN SLURRED COMPLEXES, DERIVATION 1

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
1-10	2	2	1	1	1	\ Influenza	1	1	0	0	0
11-20	5	5	3	2	0		5	1	1	3	1
21-30	18	14	6	8	3		11	4	5	2	1
31-40	17	14	5	9	3		9	3	3	2	0
41-50	16	13	5	8	9		3	0	3	0	0
51-60	6	6	5	1	3		3	1	2	0	0
61-70	3	2	2	0	0		2	1	0	1	0
Total	67	55	29	26	21		34	10	14	8	2

20 cardiac deaths, 36·3 per cent

TABLE 14—MORTALITY IN SLURRED COMPLEXES, DERIVATION 2

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
21-30	2	2	0	2	0	\ Postoperative peritonitis	2	1	0	1	0
31-40	5	5	1	4	1		4	0	1	3	1
41-50	10	8	4	4	1		7	4	1	2	1
51-60	10	8	6	2	3		5	0	2	3	0
61-70	8	5	4	1	3		3	2	0	1	0
71-80	1	0	0	0	0		0	0	0	0	0
Total	36	28	15	13	7		21	7	4	10	2

6 cardiac deaths, 21·4 per cent

TABLE 15—MORTALITY IN SLURRED COMPLEXES, DERIVATION 3

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged	No Cardiac Symptoms
11-20	2	1	1	0	0	\ Influenza	1	0	0	1	0
21-30	10	9	3	6	0		9	5	3	1	0
31-40	32	24	11	13	4		20	3	13	4	0
41-50	13	8	3	5	1		7	3	3	2	3
51-60	26	17	11	6	5		12	4	4	4	0
61-70	11	8	6	2	1		7	1	3	3	1
Total	94	67	35	32	11		56	15	26	15	7

10 cardiac deaths, 14·9 per cent

TABLE 16—TOTAL MORTALITY IN SLURRED COMPLEXES

	Total	Patients Heard From	Males	Females	Cardiac Deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac Symptoms
Derivation 1	67	55	29	26	20	36.4	34	10	16	8	2
Derivation 2	36	28	15	13	6	21.4	21	7	4	10	2
Derivation 3	94	67	35	32	10	14.9	56	15	26	15	7
Total	197	150	79	71	36	24.0	111	32	46	33	11

TABLE 17—CONTROL SERIES

Decade	Total	Patients Heard From	Males	Females	Deaths	Deaths Other than Cardiac	Living	Worse	Improved	Unchanged
1 10	2	2	1	1	0		2	0	2	0
11 20	7	6	4	2	1		5	3	0	2
21 30	30	26	10	16	5	x Exophthalmic goiter, thyroidectomy	21	9	3	9
					y y Pneumonia					
					z z Exophthalmic goiter, hyperthyroidism					
31 40	54	44	14	30	7	w Pneumonia	37	16	14	7
					x x ?					
					y y Postoperative peritonitis					
					z z Bronchopneumonia					
41 50	39	27	12	15	6	z Apoplexy	21	7	8	6
51 60	42	30	19	11	12	x x ?	18	5	8	5
					y y Peritonitis					
					z z Cancer					
61 70	14	12	10	2	4	x Cancer	8	5	1	2
					y y ?					
					z z Cancer					
71 80	1	0	0	0	0		0	0	0	0
Total	197	147	70	77	35		112	45	36	31

21 cardiac deaths 14.3 per cent

TABLE 18—MORTALITY IN T WAVE NEGATIVITY, SLURRED COMPLEXES

T Wave Negativity	Total	Patients Heard From	Males	Females	Cardiac Deaths	Mortality percentage	Living	Worse	Improved	Unchanged	No cardiac Complaints
Derivation 1	8	6	5	1	3	60.0	3	2	1	0	0
Derivation 2	0	0	0	0	0	0.0	0	0	0	0	0
Derivation 3	42	32	10	22	5	15.6	27	4	17	6	3
Derivations 1 and 2	8	6	5	1	3	66.6	1	1	0	0	0
Derivations 2 and 3	15	15	6	9	4	26.6	11	3	4	4	1
Derivations 1 and 3	0	0	0	0	0	0.0	0	0	0	0	0
Derivations 1 2 and 3	4	4	4	0	3	75.0	1	1	0	0	0
Total	72	60	27	33	17	28.3	43	11	22	10	4

In a previous article I emphasized the significance of the negative T wave in Derivation 1 alone as indicative of myocardial damage. More than one half (53.6 per cent) of the patients with a negative T wave in this group have died of heart disease. Table 9 summarizes the T wave negativity. This observation demands careful investigation.

*Slurred QRS Complexes* — This group comprises those QRS complexes in which localized thickening or slurring of the ascending or descending limb, or both, occurred. These changes are only slight departures from the normal.

Sixty-seven cases (34 per cent) occurred in Derivation 1, thirty-six (18.3 per cent) in Derivation 2, and ninety-four (47.7 per cent) in Derivation 3. Like the cases with notched complexes, the majority (43.6 per cent) were associated with preponderance of the left ventricle (Table 10).

Degenerative processes (34 per cent) and infections (35.4 per cent) occurred equally as causative disorders (Table 11).

The number of cases in which the clinical findings did not corroborate the electrocardiograms was proportionately greater than in the preceding group (forty-two cases, 21.3 per cent).

About one-third (37.6 per cent) of the cases were associated with negativity of the T wave, again largely affecting Derivation 3 (56.8 per cent). Table 12 illustrates these changes.

Only sixteen cases (8.1 per cent) of auricular fibrillation and six cases of delayed auriculoventricular conduction were recorded. Information has been received concerning 150 patients; thirty-six (24 per cent) have died from heart disease. The control series revealed a cardiac mortality of 14.3 per cent (Tables 13 to 17). A definite difference in mortality is again observed. One hundred eleven patients are alive, thirty-two are in worse condition, forty-six are improved, and thirty-three are unchanged. Eleven patients report no cardiac complaints. Table 18 summarizes T wave mortality.

#### DISCUSSION

Notching and slurring of the QRS complex, occurring in isolated derivations of the electrocardiogram, suggests a local rather than a diffuse disorder of the ventricles. Whether or not this disorder is structural cannot be stated definitely at present owing to the meagerness of necropsy material. The fact that the notched complexes in isolated derivations are identical in contour with those in the cases with involvement of all three derivations makes actual changes in the myocardium a strong possibility.

The slurred complexes are graphically less conclusive, yet they are quite sharply contrasted with the normal. Figures 7, 8 and 9 illustrate progression from slurring to notching and from slight to marked notching.

I mentioned previously that a group of cases occurred in which the clinical findings were not sufficient to identify organic heart disease, but in which the electrocardiograms definitely depicted notching or slurring of the Q R S complex (16.5 per cent of the total series). I do not believe that organic disease can definitely be excluded in this group. The majority of all the patients (82.5 per cent) had fairly good "compensation" at the time of examination, that is, they were able to be up and about with relative comfort, and no instance of general anasarca was noted. The degree of "decompensation" was recorded as 0 to 2 (on a scale of 1 to 4, minimum to maximum), while in the minority group (17.5 per cent) the grades were 3 to 4. This method of grading myocardial efficiency is, of course, inaccurate, but it permits comparative study. We are, therefore, dealing with a group of patients, whose myocardiums are quite efficient at the time of examination, and it seems possible that muscle changes, especially local disease, can be present before the grosser subjective and objective findings of myocardial disintegration become obvious.

That progression does occur is seen in the electrocardiograms of Case 252,579 (Figs 7, 8 and 9), and in the mortality statistics where the percentage in both the notched and slurred complexes nearly double those of the control series.

#### CONCLUSIONS

1 Notching and slurring of the Q R S complex in isolated derivations of the electrocardiogram must be considered as graphic entities.

2 These changes probably indicate local disorders of the ventricular myocardium affecting the conduction system.

3 Etiologic disorders occurring in order of frequency were (1) degenerative processes, (2) infections, (3) local nutritional disturbances, and (4) congenital heart disease.

4 The cardiac mortality in both the notched and slurred complexes practically doubled that of the control series.

# THE INFLUENCE OF THE EXPOSURE TO THE ROENTGEN RAY ON THE PROGRESS OF TUBERCULOSIS

JOSEPH A. WEINBERG, M.D.

OMAHA

It is generally agreed that the best method for diagnosing tuberculosis of the genito-urinary tract is by the inoculation of the urine of suspected cases into the peritoneal cavity of a guinea-pig. However, this test loses much of its practical value because of the time which must elapse before lesions are apparent in the guinea-pig after inoculation. This work has been undertaken with two purposes in view, first, to shorten the time of development of tuberculosis in guinea-pigs, so that inoculation tests will be of more practical value to the clinician, second, to determine the rôle of lymphocytes as a factor in the protection of guinea-pigs against tuberculous infection. The exposure of guinea-pigs to the roentgen ray was suggested by the favorable report of John H. Morton,<sup>1</sup> in which it is stated that, whereas with ordinary technic a period of five weeks elapses before death, with the roentgen ray exposure tubercles are apparent in ten days. Fortunately, the guinea-pig is able to withstand massive roentgen-ray treatments without apparent injury to the general system. In Morton's experiments, the animals were roentgenized for ten minutes with the Coolidge tube, with the target twelve inches from the base of the container. Five milliamperes with an eight and one-half inch spark gap was used. From 1 to 2 cc. of tuberculous urine was injected intraperitoneally.

The effect of the roentgen ray on the resistance of animals to infection has been a subject of discussion for several years. Simonds and Jones,<sup>2</sup> who were early workers in this field, concluded that mice and guinea-pigs exposed to the roentgen ray showed a greater resistance to infection than did normal animals. Lawen<sup>3</sup> found that the resistance to infection of strongly roentgenized rabbits was greatly reduced, also if the roentgen ray had not been applied for too long a time, the injection of bacteria was followed by a rise in the number of leukocytes, but with heavy doses of the roentgen ray, the injection was followed by a fall in the number of leukocytes. The cholera vibrio and typhoid

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1 Morton, J. H. J. Exper. M. **24** 419, 1916.

2 Simonds, J. P., and Jones, H. M. J. Med. Res. **33** 183, 1915.

3 Lawen, A. Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19** 141, 1909.



bacillus were used in this experiment Murphy and Ellis,<sup>4</sup> experimenting with mice, found that roentgenized animals died in the shortest time after inoculation with virulent organisms, next in order were splenectomized mice inoculated shortly after splenectomy, next were splenectomized mice inoculated eight days after splenectomy, animals inoculated eight days after splenectomy showed the same resistance as did normal animals. The most resistant animals were mice inoculated three weeks after splenectomy. Taylor and Murphy<sup>5</sup> report a series of experiments in which the progress of infection varied directly with the fluctuation of the lymphocyte count. A lymphocytosis was produced in mice by the transplantation of mouse cancer. Three mg of a culture of bovine tubercle bacilli was injected intraperitoneally. The cancer immune mice died in 477 days, while the controls died in 203 days. Also, a series of mice were immunized against mouse carcinoma and roentgenized daily for seven exposures. The roentgenized mice lived 145 days following inoculation with tubercle bacilli. The controls lived 325 days.

Simonds and Jones<sup>2</sup> found that rabbits exposed to the roentgen ray for from ten to fifteen minutes a day for three weeks, showed a steady decline in the number of leukocytes, mostly of the lymphocytes. The formation of agglutinins was appreciably lowered.

Pappenheimer<sup>6</sup> determined the effect of the roentgen ray on the lymphocyte by using trypan blue, which is a specific stain for degenerating and dead cells. Rats were exposed to the roentgen ray for fifteen minutes, killed, and exsanguinated, and the lymphocytes obtained from the thymus gland. The cells showed 23.5 per cent stained as compared with 10 per cent stained in the control.

Hektoen<sup>7</sup> exposed white rats to the roentgen ray sufficiently long to produce a leukopenia lasting from fifteen to twenty days, continuing the exposures after the injection of sheep's blood, and found that lysin formation was markedly inhibited. He regards these results as an indication that antibodies are produced in the spleen, lymphatic tissue and bone marrow, as these are the structures which suffer from exposure to the roentgen ray. A specific example would be the formation by the lymphocytes of antibodies against tuberculosis.

Against the favorable reports to which reference has been made is the work of Corper.<sup>8</sup> Following the technic of Morton, but using a culture of human tubercle bacilli instead of tuberculous urine, he found a slight involvement of the spleen and lymph nodes after thirty-

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4 Murphy, J. B., and Ellis, A. W. *J. Exper. M.* **20** 397, 1914.

5 Taylor, H. D., and Murphy, J. B. *J. Exper. M.* **25** 609, 1917.

6 Pappenheimer, A. M. *J. Exper. M.* **25** 633, 1917.

7 Hektoen, L. *J. Infect. Dis.* **17** 415, 1915.

8 Corper, H. J. *Am. Rev. Tuberc.* **2** 587 (Dec.) 1918.

one days, and a general tuberculosis after forty-eight days. He repeated the experiment, using, after the first roentgen-ray exposure, eight subsequent exposures, of five minutes duration, without shortening the time of death. The average white cell count was 2,500 per c mm., as compared with 12,000 per c mm. in the controls. Corper also used benzene injections, benzene inhalations, thorium X, Koch's old tuberculin, and ether, without increasing the susceptibility of the guinea-pig to tuberculosis. The effects of the roentgen-ray on the progress of tuberculous infection is yet an unsettled question, although it is an accepted fact that the white cells, and especially the lymphocytes, are markedly reduced by exposure to the roentgen ray. John Mackenzie<sup>9</sup> states that "it has been shown that if lymphocytes of the body are destroyed by roentgen radiation of an infected animal, the development of the infection is much more rapid." In view of the opposite conclusions arrived at by research workers, the subject is worthy of further investigation, not only for its immediate value to the clinician, but also for its bearing on the factors of immunity in tuberculosis.

In my experiments the method used by Morton has been followed, with certain variations. In all of the experiments, the inoculations were made intraperitoneally. The tubercle bacilli were grown on glycerin agar and Petroff's medium. The growth on the latter medium was the more luxuriant. The tubercle bacilli were weighed and then ground with fine sand in a mortar. All of the apparatus used was previously sterilized. The bacteria were suspended in a 0.7 per cent sodium chlorid solution, and the proper volume of suspension injected.

In the first series, five guinea-pigs were exposed to the roentgen ray, using five milliamperes of current, an eight and one-half inch spark gap, with the target twelve inches from the base of the guinea-pig container. The Coolidge tube was used. The weight of these animals, as well as five controls, was recorded. On the following day, the roentgenized guinea-pigs and the controls were each injected with 1 mg. of a third generation culture of virulent human tubercle bacilli. White blood cell counts and differential counts were made on three of the roentgenized animals and three of the controls. These blood counts were repeated in ten days, and the weights were again recorded. One roentgenized guinea-pig showed a drop in the white cell count from 15,000 per c mm. before exposure to 8,600 per c mm. ten days after exposure. The least marked drop was from 14,000 to 10,400. One of the controls showed a drop from 12,000 to 11,400, while another showed an increase from 12,000 to 12,500. The results are recorded in the tables. A majority of the roentgenized guinea-pigs showed a

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<sup>9</sup> Mackenzie, J. I. *Oxford Med.* 1: 276

loss of weight after ten days, while the controls showed no appreciable difference Two guinea-pigs of this series died on the twenty-first day, and the others of the series were killed on the same day Three of the roentgenized and three of the control guinea-pigs showed tuberculous lesions, either grossly or microscopically

TABLE 1—SERIES A WHITE CELL COUNT

	Roentgenized			Controls		
	1	2	3	1	2	3
Before inoculation	15 800	16 500	14 000	16,000	12,000	12 200
Ten days after inoculation	8,600	9,000	10,400	15,000	11 400	12,500

TABLE 2—SERIES A EXAMINED TWENTY-ONE DAYS AFTER INOCULATION

Roentgenized		Controls	
1	Killed—necropsy negative	Microscopic lesions of liver and lymph glands	
2	Killed—necropsy negative	Gross tubercles of spleen and glands Rolled omentum	
3	Microscopic lesions in lymph glands	Necropsy negative	
4	Gross tubercles in spleen, liver and lymph glands Rolled omentum	Necropsy negative	
5	Caseous lymph glands and rolled omentum	Tubercles in spleen and lymph glands Rolled omentum	

TABLE 3—SERIES A VARIATION IN WEIGHT

	Roentgenized					Controls				
	1	2	3	4	5	1	2	3	4	5
Before inoculation	350	375	325	395	315	370	390	410	350	425
Ten days after inoculation	330	290	290	400	235	400	370	395	355	405
Roentgenized guinea pigs						Average Loss of Weight				
Controls						43 gm				
						4 gm				

In this series there was no difference observed in the development of tuberculous lesions in the roentgenized and control animals, but the roentgen ray was shown to have a marked effect on the white blood cells, especially the lymphocytes, and on the weight There were two variations from the method used by Morton The exposure to the roentgen ray was fifteen minutes instead of ten minutes, and a third generation culture of tubercle bacilli was used instead of tuberculous urine

The above experiment was repeated, using the same culture, but exposing the guinea-pigs to the roentgen ray for ten minutes instead of fifteen minutes The white blood cell count was not made in this series Four roentgenized and four control guinea-pigs were inoculated after recording the weights Two of the controls died on the third day from a generalized pyogenic infection After ten days, there was no marked difference in loss of weight between the roentgenized and the control guinea-pigs At the necropsy two of the roentgenized and one

of the control guinea-pigs showed tuberculous lesions. This indicated that there was no difference in the stage of tuberculosis between the roentgenized and the control guinea-pigs.

In the next group of guinea-pigs (Series C) the exposure to the roentgen ray was increased. Four animals were exposed for fifteen minutes, the first dose being given one day before, and the second dose six days after inoculation. One mg of the culture used in series A and series B was injected. White blood cell counts made six days after the second exposure showed a drop from 13,600 to 2,200 cells per c mm in one animal, and from 14,300 to 2,800 in another.

TABLE 4—SERIES B EXAMINED TWENTY-ONE DAYS AFTER INOCULATION

Roentgenized		Controls	
1	Necropsy negative	Died on third day from pyogenic infection	
2	Necropsy negative	Died on third day from pyogenic infection	
3	Caseous lymph glands, rolled omentum	Necropsy negative	
4	Tubercles in spleen and lymph glands Rolled omentum	Caseous lymph glands	Rolled omentum

TABLE 5—SERIES B VARIATION IN WEIGHT

	Roentgenized				Controls			
	1	2	3	4	1	2	3	4
Before inoculation	360	385	360	410	Died sec- ond day			
Ten days after inoculation	295	350	345	355	Died sec- ond day			
					Average Loss of Weight			
Roentgenized guinea-pigs							43 gm	
Controls							40 gm	

TABLE 6—SERIES C WHITE CELL COUNT

	Roentgenized			Controls		
	1	2	3	1	2	3
Before inoculation	13,600	15,200	14,300	10,200	12,800	16,000
Ten days after inoculation	2,200	5,600	2,800	12,400	11,000	15,400

The differential count showed practically all polymorphonuclear leukocytes with 2 per cent lymphocytes. The controls showed from 40 to 50 per cent of lymphocytes. The blood smears, stained with Wright's stain, showed numerous fragments of basic staining material which I interpreted as being broken up white cells, since they were not present in the smears of blood from the control guinea-pigs. There was a consistent loss of weight observed which was not observed in the controls. One of the roentgenized guinea-pigs died on the twenty-fourth day, two guinea-pigs died on the twenty-sixth day, and one guinea-pig was killed on the twenty-eighth day. One of the controls died on the twenty-sixth day, one on the twenty-eighth day, and two were killed on the twenty-eighth day. Owing to an error, two of the

roentgenized guinea-pigs which died were not examined postmortem  
The other two showed tuberculous lesions

TABLE 7—SERIES C VARIATION IN WEIGHT

	Roentgenized				Controls			
	1	2	3	4	1	2	3	4
Before inoculation	390	415	295	345	325	370	325	320
Ten days after inoculation	340	300	310	340	335	355	335	295
Roentgenized guinea pigs					Average Loss of Weight			
Controls					33 gm			
					5 gm			

TABLE 8—SERIES C PROGRESS OF INFECTION

	Roentgenized	Controls
1	Killed on twenty eighth day, necropsy negative	Killed on twenty eighth day, necropsy negative
2	Died on twenty fourth day, not examined postmortem	Died on twenty sixth day, tubercles in spleen, liver and lymph glands
3	Died on twenty-sixth day, tubercles in spleen and lymph glands Rolled omentum	Died on twenty-eighth day, tubercles in spleen and lymph glands Rolled omentum
4	Died on twenty sixth day, not examined postmorem	Killed on twenty-eighth day caseous lymph glands, rolled omentum

Two roentgenized guinea pigs were not examined owing to error

Three of the controls showed tuberculous lesions and one control was negative There was no appreciable difference in the time of death between the roentgenized and the control guinea-pigs

Since there was a possibility that the roentgen-ray exposure which was given seven days after inoculation may have had a deleterious effect on the tubercle bacilli, the experiment as performed in series C was repeated, with the difference that two exposures were given with an interval of seven days, the inoculation being made one day after the second exposure Two roentgenized and two control guinea-pigs were inoculated One of the roentgenized animals died on the twenty-sixth day, the other one died on the twenty-ninth day Postmortem examination revealed microscopic lesions in both animals The controls died on the twenty-ninth and thirty-first day, respectively, both showing tuberculous lesions In these experiments the animals were injected with a known tuberculous sputum

Microscopic sections were made of the spleen, liver and mesenteric and inguinal lymph glands in those cases which showed no lesions microscopically The sections were cut in celloidin and stained with hematoxylin and eosin In only two cases not showing tuberculosis macroscopically were the lesions revealed by the microscope In two cases showing tubercles grossly, the kidneys and lungs were also examined microscopically, but neither organ showed tubercles The inguinal and mesenteric lymph glands, and the omentum were most frequently involved, while the spleen and liver, respectively, were next in the

order of frequency of involvement. The tubercles in the liver and spleen of animals not roentgenized showed large mononuclear and epithelioid cells around a necrotic center, with lymphocytes diffusely arranged peripherally. The blood vessels near the tubercles contained more than the ordinary number of polymorphonuclear leukocytes and lymphocytes, and there were a large number of these cells just outside of the blood vessels in the liver. This would seemingly indicate that the cellular elements of the tubercle are of hematogenous origin. The microscopic sections of tuberculous guinea-pigs which were roentgenized showed fewer polymorphonuclear leukocytes and lymphocytes than occurred in the controls.

Do the cellular elements of the tubercle originate from the blood or from the local tissue? Metchnikoff maintained that the tubercle is of leukocytic origin, and supposed that the giant cell and epithelioid cells are derived from the lymphocyte. This is in line with his general theory of the rôle of leukocytes. Baumgarten stated that the proliferative processes from local tissue are concerned with the function of the tubercle, basing his conclusion on the observation of mitotic figures in the local cells. Evans, Bowman and Winternitz<sup>10</sup> performed an ingenious experiment to determine the origin of the tubercle cells. They injected tubercle bacilli into the mesenteric vein of a rabbit, and then injected trypan blue into a vein. The stain showed a degeneration of hepatic endothelium, which seemed to indicate that the large mononuclear cells at the site of the tubercle are derived from fixed tissue and not from the lymphocytes.

The knowledge of the function of the lymphocyte is very indefinite. Because of the variation in classification of leukocytes it may be well to state that the term "lymphocyte" as used here includes only the small round cell leukocytes with a solid deep staining nucleus occupying most of the cell. Formerly, it was generally supposed that tuberculosis is always accompanied by a leukocytosis, and this was used as a differentiating point between typhoid fever and miliary tuberculosis. It has been observed, that with a mild tuberculous infection there is a relative lymphocytosis, but in some cases of visceral and pulmonary tuberculosis, the process is accompanied by a lymphopenia.<sup>11</sup> Warthin,<sup>12</sup> in 1896, reported two cases of tuberculosis with a marked leukopenia, in which the diagnosis was proved at necropsy. In one case, the white cell count was as low as 1,250 during the course of the disease. The differential count showed 5 per cent of lymphocytes.

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10 Evans, Bowman and Winternitz. *J. Exper. M.* **19** 283, 1914.

11 Gruner, O. C. *Biol. Blood Cells*, 1914.

12 Warthin, A. S. *Med. News* **68** 89, 1896.

## SUMMARY

I have attempted to hasten the progress of infection in guinea-pigs following tuberculous inoculation by exposing the animals to massive doses of the roentgen ray. In the first and second series of guinea-pigs there was no apparent difference in time of appearance of the tuberculous lesions in the roentgenized animals and the controls. In the third series, there was a difference of a few days in the time of death, the average time of death occurring two days earlier in the roentgenized animals than in the controls. This series received two roentgen-ray exposures. The fourth series showed the same difference in time of death between the roentgenized and the control animals, as was observed in Series C.

The exposure to the roentgen ray has had an appreciable effect on the body metabolism. It is possible that the more noticeable decrease in weight is due to the more rapid progress of tuberculosis, but post-mortem examination of the roentgenized and the control animals does not indicate this to be the fact.

The exposure to the roentgen ray has a profound effect on the leukocytes, especially the lymphocytes. A consistent drop in the white cell count and relative number of lymphocytes has been noted, the decrease being more marked in those animals subjected to more intense roentgenization. The microscopic sections of tuberculous liver tissue in the roentgenized guinea-pigs show fewer polymorphonuclear leukocytes and lymphocytes in the blood vessels than occurred in the controls, which effect is probably due to the roentgen ray.

The tuberculous lesions differ from the lesions in the controls in that they have very few lymphocytes in the outer zone. The epithelioid cells and large mononuclear leukocytes apparently are not decreased in number. There was nothing in the gross or microscopic appearance of the lesions to indicate that the tubercles in the roentgenized animals were further advanced than those in the controls. An inconsistency is noted in the frequency of tubercle formation in the spleen and lymph glands, as the lymphocytes are formed in the lymphoid follicles of the spleen and lymph nodes<sup>11</sup>. One would not expect these organs to be affected as readily as others if the lymphocytes are the main factor in combating tuberculosis.

## CONCLUSIONS

1 *Effect of the Roentgen Ray on the Life of the Guinea-Pig*—I have been unable to hasten the progress of the tuberculosis appreciably by exposure of the guinea-pig to massive doses of the roentgen ray.

2 *Effect on the Leukocytes*—The leukocytes of the blood stream are markedly reduced in number by exposure to the roentgen ray. The

reduction is proportionate to the length of exposure with a given current and voltage. The lymphocytes are most markedly affected.

3 *Origin of the Tubercle Cells*—The cells of the tubercle are probably derived both from the local tissue and from the blood. The presence of the usual number of epithelioid and large mononuclear cells in the tuberculous lesions of roentgenized guinea-pigs, where there is a marked diminution in lymphocytes, indicates that these cells are not of lymphocytic origin. The presence of an excess of lymphocytes in and around the blood vessels near the tubercles in nonroentgenized animals indicates that cells are carried to the lesions by the blood stream.



## BOOK REVIEW

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EXPERIMENTAL PHARMACOLOGY By Hugh McGuigan, Ph D, M D, Professor of Pharmacology in the University of Illinois, College of Medicine Philadelphia and New York Lea & Febiger, 1919

In his preface the author states that an attempt has been made to present experimental pharmacology in a brief, concise form, yet to give the student an adequate view of the field. The introduction and first chapter deal with general considerations of drug action, modes of drug administration and operative and other technical details. The succeeding chapters are devoted to the pharmacology of the various systems of the body, with selected experiments illustrating the action of drugs on these systems. Methods of biological standardization are described for those drugs for which these methods are commonly applied. The book is illustrated with a number of photographs, drawings and diagrams.

One criticism that might be offered is that the book contains too much extraneous matter. Thus the introductory chapters contain definitions and general statements that properly belong in a textbook of pharmacology. There is a detailed account of various methods of artificial respiration and resuscitation which seems quite out of place. There is also a considerable space devoted to statements of physiological and pharmacological facts with no accompanying demonstrative experiments.

The book should be favorably received by those teachers of pharmacology who desire to give a comprehensive laboratory course in the subject, as they will find a very large number of experiments from which to select the ones they especially desire.

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## SODIUM CARBONATE IN CHLOROFORM POISONING\*

EVARTS A GRAHAM, M D

ST LOUIS

In 1915<sup>1</sup> I described some experiments which indicated that chloroform is dissociated in the body in such a way that free hydrochloric acid is formed from it and that the toxic effects of chloroform are probably to a great extent due to the action of the liberated hydrochloric acid. The evidence on which this view was based was as follows. 1 The ease of the formation of three molecules of hydrochloric acid from one molecule of chloroform outside the body by oxidation in the presence of water suggests that also within the body in the presence of water and available oxygen the same reaction might take place. 2 Lesions in the liver similar to those which occur in chloroform poisoning can be produced experimentally with hydrochloric acid. 3 Free hydrogen and free chlorine ions were demonstrable in the necrotic areas of the liver. 4 Observations on other chlorine substitution products of methane (dichloromethane and tetrachloromethane) showed that not only did they both have the property of producing central necrosis of the liver, but that also this property was in direct proportion to the amount of hydrochloric acid which each could yield theoretically in its breakdown, i. e., that the series ran in this order  $\text{CH}_2\text{Cl}_2 < \text{CHCl}_3 < \text{CCl}_4$  in respect to the power of each to produce central necrosis of the liver. 5 Other alkyl halides of the same type as chloroform, viz., bromoform ( $\text{CHBr}_3$ ) and iodoform ( $\text{CHI}_3$ ), produce lesions in the liver and elsewhere identical to those of chloroform, and evidence was submitted that at least in the case of iodoform the analogous halogen acid (hydriodic) is formed in the body, as shown by the fact that neutral salts of this acid are excreted in the urine. 6 The property of producing central necrosis of the liver is apparently one which is common to alkyl halides in general, since ethyl chlorid, ethyl bromid, ethyl iodid and ethylene bromid all produce the lesions seen in typical chloroform poisoning; and, furthermore, that ethyl bromid and ethyl

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<sup>1</sup> Graham, E. A. Late Poisoning with Chloroform and Other Alkyl Halides in Relationship to the Halogen Acids Formed by Their Chemical Dissociation, *J. Exper. Med.* 22: 48, 1915

iodid are decomposed in such a way that hydrobromic and hydriodic acids, respectively, are formed in the body is indicated by the finding by other observers of inorganic bromin and iodin in the urine after inhalation of these substances. It was also found that the toxicity of these various substances was in direct agreement with their ease of dissociation outside the body. 7 That the property of producing liver necrosis was not dependent merely on the halogen content of the sub-

stance was shown by the fact that chloral hydrate ( $\text{CCl}_3 - \text{CH} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{OH} \end{array}$ ),

which like chloroform, has three chlorin atoms, produces relatively insignificant morphologic effects, and it is interesting that since this substance is excreted almost entirely as urochloralic acid, almost no hydrochloric acid could be formed from it within the body. 8 Sodium carbonate in hypertonic sodium chlorid solution partially inhibited the production of the lesions by chloroform. In one case it seemed to prevent the liver necrosis entirely, and uniformly its inhibitory effect on the usual swelling of the kidneys was very marked.

In a recent article by Davis and Whipple<sup>2</sup> the statements were made, "We have attempted to repeat Graham's observations on the protective action of sodium carbonate given intravenously during chloroform anesthesia," and "these experiments indicate that Graham's claims are based on incomplete or inaccurate observations. Carefully controlled experiments show beyond a reasonable doubt that carbonates given intravenously or by mouth have no effect whatsoever on the injurious action of chloroform on the liver."

Davis and Whipple used a method of experimentation somewhat different from that used in my own work, in that they administered chloroform to their dogs, for a period of one and one-half hours after a fasting period of three days, and for one and one-quarter hours after a fasting period of four days, instead of administering it for four and one-half hours to previously unstarved animals, as I had done. These authors state that they have found "that liver injury is much more uniform after a preliminary starvation, this renders the animals more susceptible to injury, hence a shorter period of anesthesia is advisable." From this we may conclude that Davis and Whipple worked with animals more susceptible to chloroform than those that I used.

Six experiments were conducted by them in all. To four chloroform poisoned dogs was given sodium carbonate in a hypertonic sodium solution, one dog received only "normal saline" solution, and another had no injection of either saline or carbonate. In my experi-

2 Davis, N. C., and Whipple, G. H. The Influence of Drugs and Chemical Agents on the Liver Necrosis of Chloroform Anesthesia, Paper II, Arch. Int. Med. 23: 636 (May) 1919.

ments, on the contrary, eight dogs and four guinea-pigs were used. To four of the dogs and to two of the guinea-pigs sodium carbonate was given in a hypertonic sodium chlorid solution, and to the remainder was given only physiologic sodium chlorid solution. The object of conducting the experiments in this way was to provide a control for each animal which received the carbonate solution. The animals were always run in pairs, that is, both of two dogs or two guinea-pigs, of approximately the same weights, were given chloroform simultaneously for the same period of time, and while one of a pair was given an injection of sodium carbonate in hypertonic sodium chlorid solution, the other animal was given an equivalent amount of physiologic sodium chlorid solution in proportion to its body weight so that each of the two animals received the same amount of fluid per kilo. After completing the administration of the anesthesia, both animals of a pair were put under identical conditions as to diet, etc., and both were sacrificed at the same time (two days after the experiment). It was felt that this method would provide the best means of controlling the experiment because it afforded in each case a direct comparison of animals which had been subjected to identical conditions, with the single exception that one animal received sodium carbonate and the other did not.

In my experiments conducted in this manner it was found uniformly that the animals which received the alkali had less necrosis than their controls, and in one case no necrosis at all occurred. It was also noteworthy that the alkali animals seemed less toxic, and at autopsy other changes characteristic of chloroform poisoning, as well as the liver necrosis, were less conspicuous than in the control animals. In spite of the statement of Davis and Whipple that "carefully controlled experiments show beyond a reasonable doubt that carbonates given intravenously or by mouth have no effect whatsoever on the injurious action of chloroform on the liver," I must disagree with them for the following reasons:

In their work, only two dogs were used for control purposes. These control animals were both dogs which had been given toxic doses of chloroform only a short time before (twenty-five and eleven days, respectively). Thus, these two served both as experimental and as control animals. It should be stated in this connection, that Davis and Whipple, instead of sacrificing the animals at the end of two days, merely removed small pieces of their livers and allowed the animals to remain alive. They consider that complete regeneration of the chloroform poisoned liver may safely be assumed to have occurred in this period of time, basing their decision on earlier experimental results. They do not demonstrate that it actually was complete in these particular dogs, and it is on this supposition very largely that

they question the validity of my results. Moreover, of the two control dogs, one received sodium chlorid solution intravenously, whereas the other received nothing, so that there was only one control of the carbonate experiments in the manner in which I had tried carefully to control all of mine.

Again, it is to be remarked, in reading the protocols of the experiments of Davis and Whipple, that in one of the carbonate experiments a note is made that "one of the old incisions has a superficial discharging pocket," and in another one that the dog is "recovering from distemper." It has been a frequent observation that infections, like all other conditions which remove glycogen, increase the susceptibility of animals to the toxic effects of chloroform, and for that reason it would seem unfair to draw conclusions from these dogs. Furthermore, it is noteworthy that the diets after the administration of the chloroform were extremely varied, for example, of the carbonate dogs, two had a "fat diet," one had a "casein diet," and nothing is stated about the diet of the fourth dog. Of the two controls, one had a "lean meat diet," and no information is given about the diet of the other. Moreover, even considering their experiments as recorded in their protocols, it is to be remarked that half of the dogs which received carbonate showed, as a matter of fact, less necrosis than one of the two controls.

Davis and Whipple are apparently inclined to consider the liver necrosis as the only important change produced by chloroform poisoning, as they ask "why chloroform passes by all body tissues until it reaches the liver, where the hypothetical chemical reaction takes place with release of hydrochloric acid." My position, however, has always been that although the liver is, perhaps, the most conspicuously affected organ, it is by no means the only one. In fact, Whipple's earlier articles directly controvert the idea of a specific susceptibility of the liver, inasmuch as he has shown in his own experiments that other tissues are affected to a sufficient degree to show pathologic changes.<sup>3</sup> The fact, for example, that the kidneys and heart muscle are markedly affected is so well known and has been observed so frequently by others that it would seem unnecessary to call attention to it again. I do not agree, therefore, that the liver necrosis is the only important change produced by chloroform poisoning. But I still hold the opinion that, since the decomposition of chloroform into three molecules of hydrochloric acid is an oxidation process in the presence of water, it is not surprising, in the light of the theory that the liver should show most conspicuously the anatomic changes of chloroform poisoning, in view of the fact that the liver is an organ in which oxidation processes are very active, and perhaps more active than elsewhere in the body.

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3 Whipple, G. H., and Sperry, J. A. Chloroform Poisoning. Liver Necrosis and Repair, *Bull. Johns Hopkins Hosp.* 20: 278, 1909.

This fundamental difference in assumption regarding the specific susceptibility of the liver to chloroform is of the greatest importance because it was possible to show that not only did sodium carbonate in hypertonic saline solution inhibit the necrosis of the liver, but that it diminished also the swelling of the kidneys. For example, on page 61 of my article referred to<sup>1</sup> it is stated, under experiment 3, that although there was a difference of weight between the two dogs at the beginning of the experiment of only one-half kilo (the weights being 4.5 and 5 kg, respectively) the respective weights of the kidneys at the time the dogs were sacrificed were 43 gm and 68 gm, a difference of 25 gm, that is, the kidneys of the dog which received the carbonate weighed only 43 gm as contrasted with 68 gm for the control. Likewise, the kidneys of the control dog were swollen and gray in appearance in contrast to a practically normal appearance of the kidneys of the carbonate dog. Moreover, in experiment 4, although the carbonate dog weighed 0.2 kg more than the control (2.7 kg and 2.5 kg, respectively), the former's kidneys actually weighed 9 gm less than those of the control when the dogs were sacrificed. MacNider has corroborated my findings of the protective action of sodium carbonate on the kidneys in experiments in which he produced chloroform intoxication of dogs which had been rendered nephropathic by uranium nitrate. He states<sup>4</sup> "The protection of the kidney by the carbonate, which is shown by the kidney being functionally much more active during an anesthesia than the kidney of a control animal, and by the lack of fatty degeneration, acute swelling, and necrosis of the renal epithelium which is constantly seen in the unprotected kidneys, is probably dependent on two factors: the neutralization of organic acids formed prior to and during the anesthesia, and the neutralization of hydrochloric acid which Graham has shown to be liberated by chloroform during an anesthesia induced by this substance." The anesthetic substance which he used was Gréhant's mixture which depends chiefly on chloroform for its anesthetic properties. Again, in a more recent article, he concludes as follows<sup>5</sup> "A solution of sodium carbonate equimolecular with a 0.9 per cent solution of sodium chloride when given intravenously to anesthetized naturally nephropathic animals confers a variable degree of protection to the kidney."

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4 MacNider, William de B. The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate, and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anesthetic by Sodium Carbonate, *J Exper Med* **23** 171, 1916

5 MacNider, William de B. The Stability of the Acid-Base Equilibrium of the Blood in Naturally Nephropathic Animals and the Effect on Renal Function of Changes in This Equilibrium. II. A Study of the Efficiency of an Alkali to Protect the Naturally Nephropathic Kidney Against the Toxic Effect of an Anesthetic, *J Exper Med* **28** 517, 1918

Davis and Whipple state also, that in my work "it was found that central liver necrosis followed the use of (1) dichlor- and tetrachlor-methane (in proportion to chlorine content)" Particular pains were taken in my article to state that the chlorine (or halogen) content of the molecule had nothing whatever to do with the production of the lesions, but that rather it was the production of the respective halogen acid from the molecule which was important On page 68 of my article, the statement is made, "These results seem to afford striking confirmation of the idea that the essential factor in the production of these severe lesions by alkyl halides is the halogen acid formed by decomposition rather than merely the halogen content of the molecule," and again on pages 68 and 69, "Moreover, that the mere presence of halogen atoms in the molecule is not the responsible factor is demon-

strated by the fact that chloral hydrate ( $\text{CCl}_3 - \text{CH} \begin{array}{l} \diagup \text{OH} \\ \diagdown \text{OH} \end{array}$ ), which,

like chloroform ( $\text{CHCl}_3$ ), possesses three chlorine atoms, produces relatively insignificant morphologic effects Some other factor must therefore be responsible Evidence has been submitted to show that an important factor is probably the halogen acid (hydrochloric, hydrobromic, or hydriodic acid) which is formed by chemical dissociation of the alkyl halides within the body That these substances form their respective halogen acids in the body is shown by the occurrence in large quantity of the neutral salts of these acids in the urine In this respect they differ from chloral hydrate, which is excreted mainly as urochloralic acid, and of which therefore only a small portion is decomposed to give neutral chlorides"

Again Davis and Whipple state (p 649), "In an article published in 1912, Graham makes the statement that chloroform is one of a group whose effect on organs is like that of asphyxiation He has later amplified this statement with the suggestion that many common anesthetic substances, including chloroform and ether, also carbon monoxide and potassium cyanide, are capable of dissociating in a manner which yields bivalent or unsaturated carbon It is easy to imagine that such compounds might then appropriate oxygen within the body, in order to satisfy their free bonds" It was natural to think of the possibility of the direct union of bivalent carbon with oxygen at the time my article in question was in preparation But the idea was dismissed because there is little or no evidence to support it, at least as regards a group reaction In fact, Burker,<sup>6</sup> as early as 1910, suggested the possibility that the suppression of oxidations during narcosis is due to the appropriation of oxygen by the anesthetic substance This

<sup>6</sup> Burker Eine Neue Theorie der Narkose, Munchen med Wchnschr 57 1443, 1910

whole question, of course, involves a consideration of many factors of which one is a difference in oxidation potential between the narcotic substance and the countless other substances in the cell which are oxidizable. As Verworn<sup>7</sup> has pointed out, in so far as narcotic substances as a class are concerned, carbon dioxid offers one serious difficulty to such a belief because of its inability to be further oxidized.

It is not to be expected that absolute inhibition of chloroform liver necrosis can uniformly be obtained by the use of such an alkali as sodium carbonate, for the reason that this substance gains entrance to the cell with difficulty. On page 59 of my article the statement is made "The degree of inhibition of the necrosis was subject to wide variations in the different experiments." Also on the same page attention was called to the fact that only once was complete inhibition obtained. This fact serves to emphasize all the more strongly the need of controlling the alkali experiments carefully. In this connection the recent excellent work of Lynch, Smith and Marshall,<sup>8</sup> on "mustard gas" poisoning is of very great interest. For they also come to the conclusion that the chief toxic effects of mustard gas are to be ascribed to the hydrochloric acid liberated from the mustard gas within the body. Also, as in my own work, these authors found that an inorganic alkali (sodium bicarbonate), partially inhibited the toxic effect but not to uniform degree in all their experiments.

Because, however, Davis and Whipple disagree with my former results with sodium carbonate, it seemed desirable to perform another experiment. Two normal adult dogs were placed in adjacent cages for three days preceding the experiment and were given a liberal allowance of meat, bread and water. They were then given chloroform (Mallinckrodt's "Purified for Anesthesia") for four hours, by inhalation, and kept as nearly as possible at the same depth of narcosis. Immediately before the anesthesia Dog A weighed 7,240 gm and Dog B weighed 5,675 gm. During the anesthesia Dog A received 239 c c of Fischer's hypertonic sodium carbonate solution ( $\text{Na}_2\text{CO}_3$ , 10,  $\text{H}_2\text{O}$ , 10 gm,  $\text{NaCl}$ , 14 gm, distilled water, 1,000 c c), which was the same solution and the same proportionate amount as used in my earlier work. To Dog B was given an equivalent amount (187 c c) of sterile physiologic sodium chlorid solution (0.85 per cent.  $\text{NaCl}$ ). In both instances the solutions were warmed to body temperature and injected slowly into the external saphenous vein. After being returned to their cages, both dogs were allowed meat, bread and water freely. On the following day Dog A (alkali) was found to be lively and responsive,

<sup>7</sup> Verworn. Irritability, Yale University Press, 1913, p. 260.

<sup>8</sup> Lynch, V., Smith, H. W., and Marshall, E. K. On Dichlorethylsulphid (Mustard Gas). I. The Systemic Effects and Mechanism of Action, J. Pharmacol. & Exper. Therap. **12**:265, 1918.



but Dog B (control) lay curled up in his cage Dog B had vomited several times, but no vomited material was seen in Dog A's cage Dog B died twenty hours after the completion of the administration of the chloroform

Four hours later (twenty-four hours after terminating the chloroform administration) Dog A was killed with chloroform, and both animals were immediately examined at necropsy While being given the chloroform to kill it Dog A (alkali) was sufficiently active to struggle vigorously Very marked gross differences were found in the appearances of the organs The liver of Dog B (control) was very edematous and yellowish cream colored, as if it contained an enormous amount of fat On the other hand, Dog A's liver was purplish red in color and contained apparently only a moderate amount of excess fat Also, the kidneys of Dog B were gray in color and were clearly more swollen than those of Dog A The comparative weights of the organs were very interesting Although Dog B (control) weighed 1,600 gm less than Dog A (alkali), its liver weighed 6 gm more (270 gm and 264 gm, respectively) than that of Dog A, and its kidneys weighed 5 gm more (43 gm and 38 gm, respectively)

The greater weight of Dog B's organs was interpreted as being due probably chiefly to increased edema To determine this point more accurately, however, a portion of the liver of each dog was evaporated to dryness on a steam bath, and the water content of both A's and B's livers was found to be 73.6 per cent and 79.5 per cent, respectively In other words, therefore, the liver of the control dog had a water content 6 per cent greater than that of the dog which received alkali Microscopically, also, there was a marked difference in the amount of necrosis in the two livers In Dog B the necrosis was practically complete throughout the whole section with scarcely any parenchymatous cell which seemed even fairly normal In Dog A (alkali), on the contrary, although the necrosis was marked, it varied in amount in different lobules from an involvement of from three-fourths to four-fifths of the lobule At the periphery of each lobule there was a border of several rows of parenchymatous cells which were practically normal, except for some fat vacuoles Dr Opie very kindly examined the livers of both dogs for me, both in the gross and from the microscopical slides, and he has permitted me to state for him that the difference in the amount of necrosis in the two livers was so striking as to be unquestionable This experiment, therefore, is confirmatory of my earlier work, and it shows that dogs may be protected to a variable extent from the effects of late chloroform poisoning by the administration of sodium carbonate

Finally, it should be said that the failure to obtain complete inhibition nor even uniformly striking inhibition of chloroform necrosis of the liver by alkali, does not constitute a serious objection to the idea that the toxic effects of the alkyl halides are due largely to the action of halogen acids liberated from the respective substances. The large amount of other evidence for the idea which is summarized in the opening paragraph of this article cannot be controverted by the mere fact that sodium carbonate will not always completely inhibit chloroform necrosis of the liver.

# A STUDY OF MULTIPLE CARTILAGINOUS EXOSTOSIS

## FOUR CASES WITH REPORT OF CALCIUM AND MAGNESIUM METABOLISM IN TWO CASES

JAMES A HONEIJ, M D  
NEW HAVEN, CONN

The first case was seen by me in 1912 in the service of Dr Francis H Williams at the Boston City Hospital, since which time several cases have been studied. Early in 1917 a case in New Haven came under observation and was referred to me by Dr William F Verdi. It was studied essentially for calcium and magnesium balances in conjunction with Drs Frank P Underhill and Jean L Bogert. Eighteen months later a second case was studied, and the results compared with those found in the first case. During this time, two other cases were under observation but no study of the calcium and magnesium metabolism was made.

This report covers the complete examination of four cases, from a clinical, osteologic and roentgenographic point of view and includes the metabolic results in two of them. A pathologic report of a growth removed in one case is also attached.

A brief review of the literature is given here and an analysis showing the bones affected in sixty-six cases, as well as other information bearing on the questions brought out by this investigation.

### REPORT OF CASES

CASE 1—R B, American, born in Connecticut, aged 22, male, single, occupation, clerk. Outpatient. March 7, 1918.

*Diagnosis*—Multiple exostosis.

*Complaint*—None, except pain off and on up until two years ago.

*Past History*—Patient is one of six children—three brothers and two sisters. Weight at birth, 7 pounds, normal delivery, breast fed. Had chicken pox, measles and whooping cough as a child.

*Present History*—At birth, feet were flexed upward against lower legs. These gradually came down and patient was able to walk normally at 1 year of age. Slight impediment of speech was noticed in early life. He lisped, pronouncing "c" and "s" as "th". At 2½ years of age he was taken sick during the summer and had chills every day, followed by fever and aching feeling. These chills did not occur at regular hours each day—thought to be malaria. When 7 years old (listless and did not play) a doctor was called who examined him, finding his knees, ankles, legs and wrists swollen and prominent but not painful. Was given lime treatment and nourishing foods. He improved rapidly. From then up to his tenth year he had whooping cough, measles and chicken pox. Since then he has had no disease. As a young boy, he played the usual games, but noticed that his limbs ached on rainy days. Photographs at 2½ and 7 years of age show a distinct asymmetry of face. There is also a slight deviation of the hands so that the radial styloid process is prominent.

Patient has no complaint, except that he tires easily on working much. Appetite normal. When examined for the draft his weight was 100 pounds stripped. At present date he weighs 111 pounds without coat and vest.

*Physical Appearance* — Rather poorly developed and undersized individual. Narrow and slightly built with rather prominent bones. Is knock-kneed, his left leg being especially curved, flat-foot, ankles are prominent. It is noticed that his forearms and lower legs are much shorter in proportion to the rest of his body (Fig 1). Hips are narrowed. Chest is flattened and the ribs are quite prominent. Distinct bone protuberances on upper bones, especially ante-

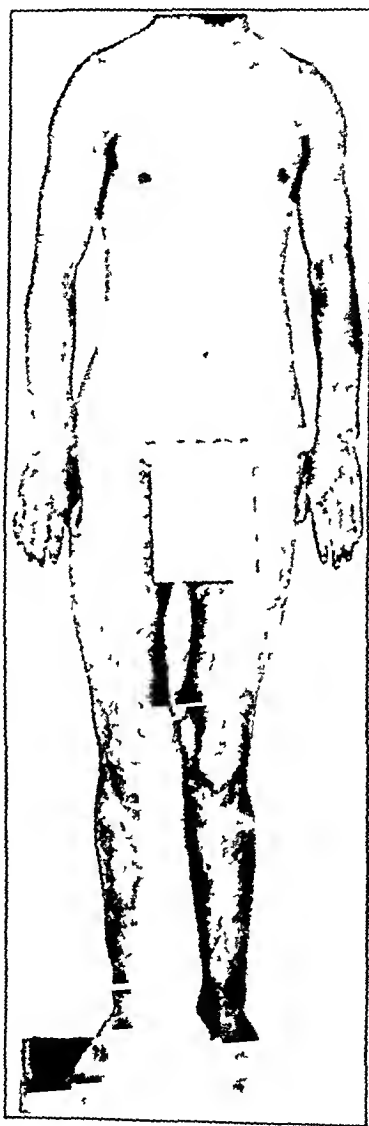


Fig 1—Case 1, R. B. The forearms and lower legs are short in proportion to the remainder of the body. The hips are narrow, the ankles prominent, knock knees, especially the left.

rior surface right thigh. Hands are short and there is marked disproportion in length of fingers. Face is distinctly asymmetrical. Distinct bony protuberances are felt around upper arm and lower thigh (Fig 2), also marked irregularity of the ribs. The wrists are enlarged and very irregular, as are also the knees and ankles. Motion of shoulders, wrists, knees and ankles is decidedly limited. There is nothing else of particular note.

Lung and heart examination is negative. Skin is normal, although rather dry. The examination of the mouth shows unusually high palate and there is a distinct deviation of the septum.

*Röntgenographic Examination—*

Skull (Not obtained)

**Vertebral Column** There is a lateral curvature and slight kyphosis. Vertebrae are not large and the upper five dorsals show a greater transparency than is usual. The first, second and third dorsals appear somewhat compressed.

**Ribs** The thorax shows marked asymmetry (Fig 3). The ribs show a most unusual increase in their downward angle or direction. This is especially true of the six upper ribs. The ribs themselves are bowed, the upper six, except the first, are considerably narrower than the others. Anterior processes are decreased and in some places are practically obliterated, the ribs overriding one another. There are no definite exostoses.

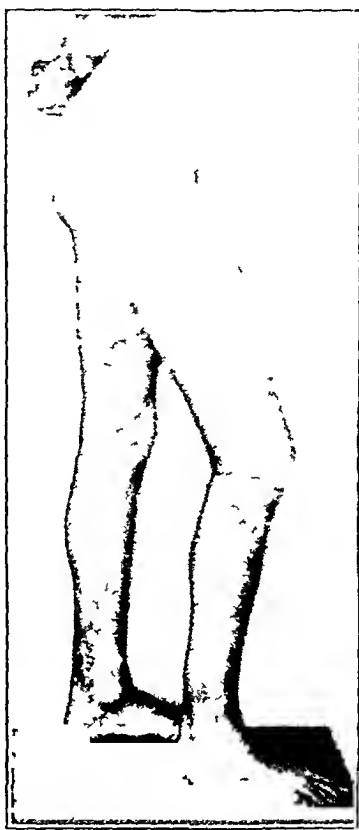


Fig 2—Case 1, R B Protuberance on anterior surface of right thigh

**Clavicles** Are considerably bowed, even in diameter throughout, heavy, show no exostoses.

**Scapulae** Of normal proportions. The right is somewhat irregular in outline at its outer border. The acromion processes are rather large. Glenoid fossae are rather shallow, small, especially so when compared with the size of the heads of the humeri, especially the left.

**Pelvis** Is small. Lower portions, including the os pubis and ischii, show a rotated development. All the bones appear poorly formed, irregular in shape and outline. There are definite outgrowths on the iliae and the os pubis is bowed and much increased in width. The symphysis pubis is somewhat increased in width. The sacro-iliac synchondrosis is extremely irregular in outline. The left acetabulum is irregular in outline and the right somewhat shallow. The density of the pelvic bones, especially the lower portions of the ilii is somewhat increased. The pelvic cavity is asymmetrical.

**Humeri** Right, approximately 31 cm in length Left, approximately 28 cm long Ends are very large and the neck on the left side is also much increased in width The width of the head on the right is approximately 4.5 cm and on the left approximately 5.5 cm The shaft is approximately 3 cm on the right and 2.7 cm on the left There are definite exostoses on the middle of the shaft on both sides, and on the left between the middle and the head, posterior surface The bone is heavy and shows no transparency as has been evident in some of the other cases The joint surfaces are apparently clear Epiphyseal lines are barely discernible

**Radius and Ulnae** Extremely bowed, so much so that the radius crosses the ulna at its upper third (Fig 4) Approximate length is 21 cm on the right, 20.5 cm on the left The ulna is 21 cm on the right and 23 cm on the left The articulation is very free between radius and ulna Bones are somewhat increased in width and proportion The lower ends of the radius show the greatest increase in width The bone is affected for approximately 8 cm on the left and practically the whole length on the right There are



Fig 3—Case 1, R B Asymmetry of thorax, bowing of ribs, small scapulae and large humeri

small exostoses The ulna shows the same changes excepting the greatest increase in width is at its proximal head The lower ends, however, are considerably deformed, are somewhat transparent and show exostoses The styloid processes are not developed The epiphyses are not determined Joint spaces are clear

**Femora** The length of the femora is not determined They are approximately from 53 to 56 cm in length The left femur is somewhat heavier and wider than the right The right, however, shows the greatest deformity and the only definite cauliflower-like exostosis (Fig 5) Greatest width, head of right femur, is approximately 8 cm and the left 8.5 cm Appearance of the ends is clublike, with irregular outline, enormously widened neck and although showing irregular growth, shows no definite exostoses The exostosis on the right shows a definite outgrowth, continuous with the bone, is some 5 cm in length by 3.5 cm in width There appears to be little cartilage and its density is even greater than that of the normal bone Above this growth are two similar rounded, prominent processes, one of which appears as an outgrowth from



Fig 4—Case 1, R B Disproportion between radius and ulna, radius is curved styloid process is rounded, exostoses, disproportion of carpal bone



Fig 5—Case 1, R B Cauliflower exostosis on femur

the cortex (Fig 6) The lower ends of the condyles appear to be somewhat squared, surface slightly flattened, but otherwise within normal limits The bones do not appear to be transparent but the longitudinal striations as normally seen are very irregular and also irregular in density The epiphyses of the heads are clearly discernible The condyles, however, are not seen

**Tibia and Fibula** The right tibia is 36.5 cm in length and the fibula 34 cm This is not the true length of the fibula as it apparently fuses with the tibia about 8 cm above its lower end At this point the tibia is 4.5 cm in width, whereas, through the malleoli it measures only 6 cm in width The middle of the shaft is 2.5 cm in width The head is 8 cm The head of the fibula is 3.5 cm in width and just below the head the width is 3 cm The

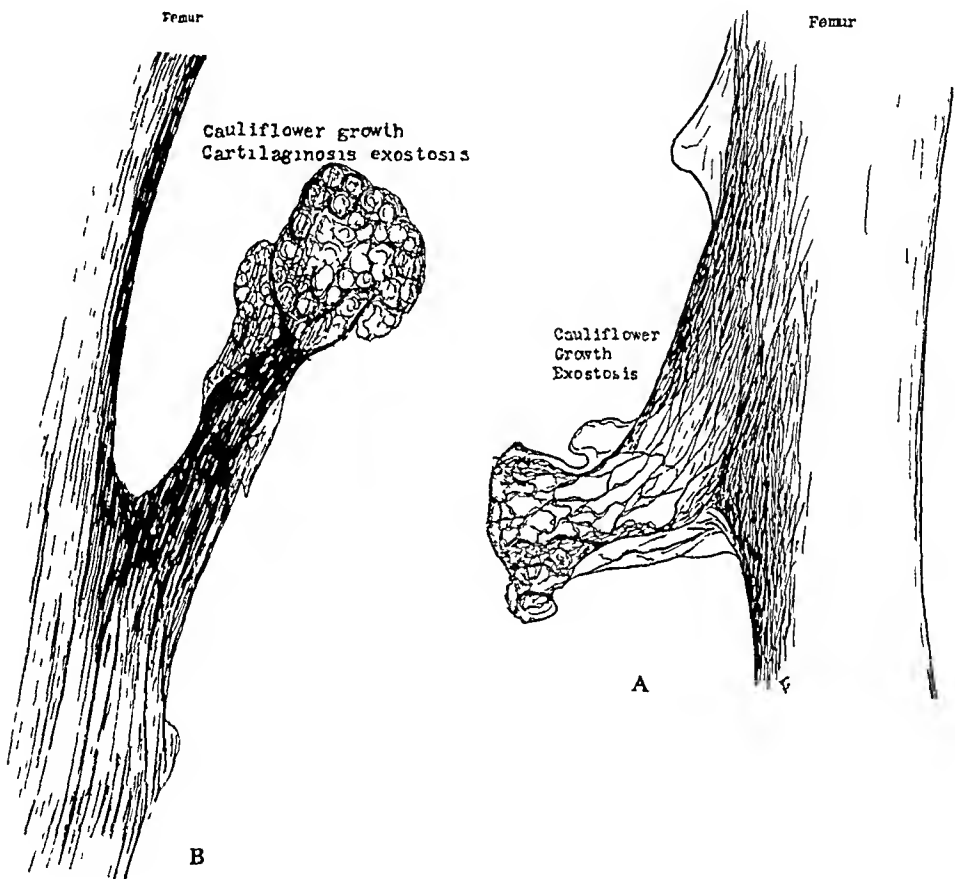


Fig 6—Cartilaginous exostoses, cauliflower growth, on femur

middle of the shaft is 1 cm and the lower end is 3 cm The left tibia is 36.5 cm and the fibula is 32 cm in length The fibula is fused to the tibia at its upper and lower extremities by a clublike formation which is approximately 6 cm in length The tibial head is 8 cm wide, middle of shaft is 2.5 cm and the lower end is approximately 5 cm, with the fibula which is fused to it, it is approximately 7 cm At the upper extremity where the fibula and tibia are fused the width is 7.5 cm The fibula, middle of shaft, measures 1.5 cm Width of the ends is not determined Bones show very little transparency, rather heavy penciling and longitudinal lines There are distinct growths as part of the bone, although on the right the fibula just below the head shows an exostosis which apparently arises from the cortex which shows as a heavy opaque line, about 2 cm in width Bones are slightly bowed,



except the left fibula. The epiphyseal lines are not determined. Joint space is clear. Tibial heads are not massive but show some surface flattening (Fig 7).

Lateral view of right tibia, 8 cm from lower end, shows a very marked boblike exostosis which has pushed into the fibula, has bent it backward and has directly interfered with its growth. It is this point which appears as a fusion on the anteroposterior view. The lower end of the fibula, however, is distinctly fused with the tibia (Fig 8).

**Hands. Carpals.** The os magnum is enormously developed as compared with the other bones. All the bones are somewhat irregular in shape.



Fig 7—Case 1, R. B. Anteroposterior and lateral views of tibiae and fibulae.

**Metacarpals.** Show the usual disproportion in length. The longest bone of the right hand is the second metacarpal which is 62 cm long. The first is the shortest. It measures 4 cm, the third, 57 cm, the fourth, 58 cm, and the fifth, 5 cm. The ends of the bones are somewhat increased in width, especially the second metacarpal. The changes, however, are slight, as compared with the other bones. The longest bone of the left hand is the second which measures 65 cm, the shortest is the first which measures 42 cm. The third measures 63 cm, the fourth measures 55 cm and the fifth 54 cm. The third metacarpal shows some increase in width throughout and the second and fourth show small exostoses.

**Phalanges** A few of the bones show some increase in width, are irregular in form and show small exostoses. Penciling is very distinct. There is also disproportion in length. Joint spaces are clear. The epiphysis is not determined in any of the bones, either phalanges or metacarpals.

**Feet** The length of the metatarsal bones is increased and they are disproportionate in length. They show a few small exostoses, changes are not marked. Phalanges also show deformities, change in shape, size and length, with exostoses on several. Some penciling of the bone is seen. Joint surfaces are clear. Epiphyseal lines are not determined.

**CASE 2**—E D, female, Italian (born in the United States), aged 16, occupation factory helper, entered dispensary, Jan 9, 1917

*Diagnosis*—Chorea Exostosis

*Complaint*—Mother states that patient has dropped dishes and knife and fork when eating. Facial distortion and funny motions with arms and legs since four weeks ago. At present patient is hardly able to walk. Patient has to be dressed, in fact put to bed and fed by her family.

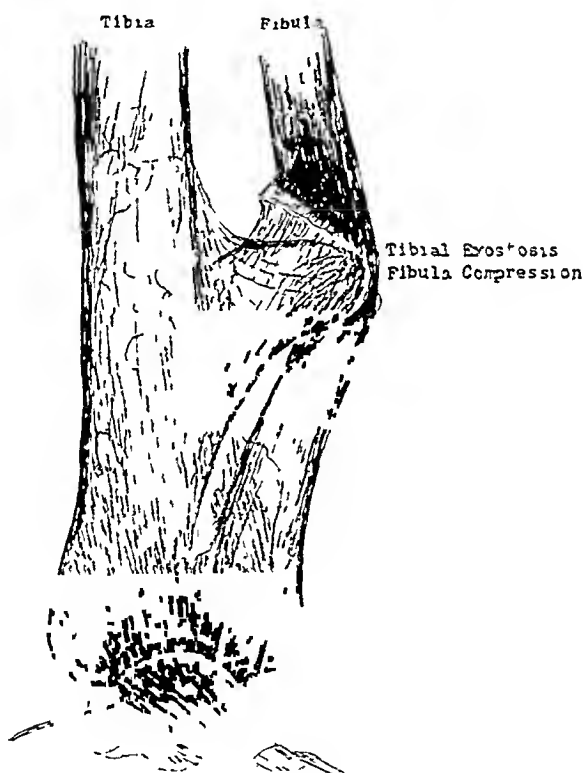


Fig 8—Case 1, R B Tibial exostosis with compression of fibula

*History*—Patient and family have noticed during last few years lumps on different parts of body, especially left arm just below shoulder. These have caused no alarm and little attention. Patient has been unable to raise the left arm to comb her hair.

*Past History*—Never has been ill.

*Family History*—Parents alive and well. Negative.

*Physical Examination*—Patient is noticeably short of stature, walks with a curious short step, automaton-like. Motion of arms and legs is decidedly limited. Skin is dark but clear. Lungs and heart are negative. The skeletal examination shows marked changes. Both large and small, more or less hard, irregular masses are felt on different parts of body, mainly near head of humerus, wrists, knees and ankles. Hands and feet are small and show difference in length of toes and fingers. More detailed information could not be obtained. Weight, approximately 100 pounds. Height, approximately 5 feet.

*Röntgenographic Examination*—Skull Diameters apparently within normal limits There is no disproportion between the skull and face Teeth show normal dentition Sinuses are small Bones in general of normal density Tables of skull of normal width Sutures, circulatory depressions and intercranial density within normal limits Sella turcica is small The clinoid processes closely approximate each other

*Vertebral Column* Cervical vertebrae within normal limits Dorsal and lumbar vertebrae, although small, are well shaped, within normal limits There is a slight lateral curvature lower dorsal region The sacrum is small, vertebral diameter much increased Density and outline irregular, but no definite exostoses seen

*Ribs* Show some bowing and increased downward angle from the vertebral articulation The anterior ends of the bone are slightly irregular, somewhat enlarged and widened and there are definite exostoses on the first, second and third ribs, left Thorax slightly cone-shaped, narrow Vertebral diameter increased

*Clavicles* In general length and shape, clavicles appear to be normal Ends, however, are considerably increased in width and are porous and irregular in outline At least 4 cm of the distal end of the right and 3 cm from the end of the left are distinctly thinned There is an exostosis, lower surface 3 cm from the distal end on the right

*Scapulae* As far as can be determined show very few changes, except in the glenoid and axillary borders of both scapulae These are irregular and there are definite periosteal elevations and exostoses on the right On the vertebral borders of the left, at the lower end, there are exostoses also Acromion ends are somewhat porous, on the left they are slightly enlarged

*Pelvis* Bones of the pelvis are small, flattened, somewhat distorted Iliac crest shows some irregularity The epiphysis is still ununited The epiphyseal line is slightly irregular Exostoses occur on both sides, middle upper A small exostosis occurs on the left outer border just above acetabulum Another small exostosis occurs on the right at the lower sacro-iliac synchondrosis inferior surface The os pubis is very large, increased in width, irregular surface and in marked contrast to the os ischii Small areas of periosteal elevation closely resembling exostosis are seen At os ischii on the right, below the acetabulum anterior surface, is a small exostosis

*Humeri* Right humerus is 23.5 cm in length, width of head through epiphyseal line 4 cm Width of condyles 5 cm Middle of shaft 2.5 cm Left epiphysis 4.2 cm Width of condyles 5 cm Middle of shaft 1.8 cm In the upper half of both bones the changes are marked Bone is increased in width below the epiphyseal line The outer border on the right is irregular and the cortex is not visible The inner upper left border is also irregular Definite exostoses occur on both the inner and outer surfaces, definitely on the shaft—on the right, 5 cm and 8 cm below the epiphysis and on the left, 3.5 and 7.5 cm below the epiphysis The upper half of both bones are but slightly porous and the processes distinctly merged with the bone proper The lower half of both bones appears to be normal

*Radius and Ulnae* Right, 17 cm in length Left, 14.3 cm in length Right ulna 20 cm in length, left ulna 17.4 cm in length From these measurements it is evident that there is a great disproportion in length between the two arms (Fig 9) Ends are enlarged but not to such a marked extent as in the tibiae and fibulae Ulna is not as much affected as the radius The shafts show some periosteal thickening and the ends are affected for a distance of (right upper) 3 cm, (right lower) 5 cm, (left upper) 3 cm, (left lower) 4.5 cm Longitudinal penciling is beautifully demonstrated The epiphyseal lines are very definite, the ends are not united except for the left lower radius where union has taken place and the epiphysis is just as much affected as the lower diaphysis Small exostoses are seen on ends of all these bones Joint spaces are clear There is no bowing of the bones The styloid processes are noticeably stunted and rounded

Femora Right Total length of the bone from the head to the lower articular surface is 37.5 cm. Left is more difficult to determine but is approximately 38 cm in length. The ends of the bone are affected for approximately 10 cm above and below (on the right). On the left, the bone is affected for approximately the same distance. This leaves only about 15.6 cm of the shaft unaffected. The greatest changes are seen in the neck which is tremendously increased in width (Fig 10). The angle is diminished and the ends appear deformed. Numerous lines are visible indicating exostoses, some of which are considerably denser than the bone and others are transparent.



Fig 9—Case 2, E D Radius and ulna, no bowing. Marked disproportion of carpal bones.

Growths at the lower ends of the bone are mostly transparent. These growths are also somewhat different from the ones previously described as there seems to be a base line as heavy as the cortex in some instances, in which the growths distinctly arise. The middle of the right femur is 1.8 cm, the upper end is 6.3 cm and the lower end 6.5 cm wide. Left upper is approximately 8 cm wide, lower 7.5 cm. Joint spaces and articular outlines are clear. Very few changes are seen in the lower epiphyses of the femora. The epiphyseal lines are discernible but not at the head of the femur. Some of the growths are apparently crowned entirely by cartilage as they gradually fade away on the roentgenograms. Lower end lateral view of femora shows some of these

exostoses to be enormous, with definite stalactite processes. Some of these growths are 3.5 by 5 cm and the stalactite processes 5 cm and more in length.

**Tibiae and Fibulae.** Right tibia 29 cm in length. Fibula 25 cm in length. Left tibia 28.7 cm, fibula 25 cm. There is marked contrast between the ends of the bones and the shaft. For a distance of 10 cm right upper, the tibia is much increased in width and on the left for a distance of 6 cm. Lower ends, approximately 5 cm of bone show the same changes (Fig 11). The epiphyseal line is discernible but shows an increased deposit. In the areas affected the cortex is not discernible. The bones show beautiful penciling, longitudinal striations and the lateral surfaces show definite exostoses.

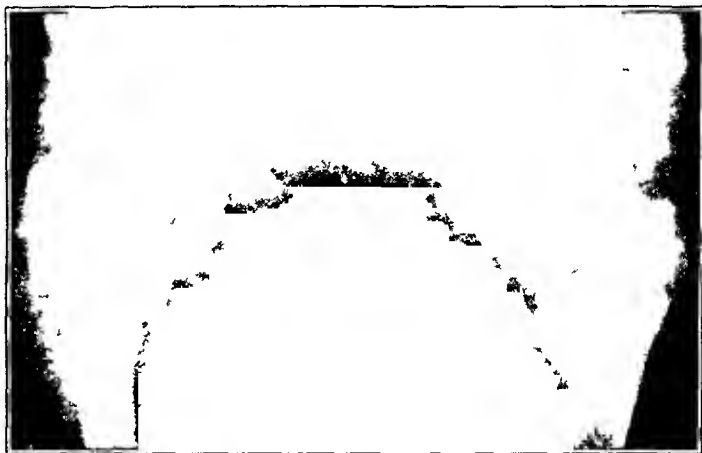


Fig 10—Case 2, E D Asymmetry of pelvis with enormous enlargement of upper end of femur



Fig 11—Case 2, E D Lateral and anteroposterior views of lower end of tibia and fibula and tarsus. Exostoses on tibia and fibula. Disproportion of tarsal bones.

These are somewhat more transparent than the bone itself. These growths are not imposed on the cortex but appear to be part of the general growth of the ends. The fibulae show greater changes than the tibiae. The right fibula, middle of shaft, measures 12 cm and the upper head 3.5 cm. The lower measures 3 cm. This increased width extends for 5 cm above and 7 cm below. The shaft is somewhat increased in width and there is some periosteal change at the ends of the bone. They show a greater increase in transparency and the lines run in all directions with superimposed lines from the growths. There is a definite irregular outline to the bone with definite exostoses. Left

fibula The ends show greatest changes The shaft is not as much affected The width of the middle is 9-10 cm The ends measure 4 cm above and 2 cm below The upper end is affected for a distance of 5 cm and is similar in appearance to the right The lower end is less affected The bones are not bowed The epiphyses of the fibula do not show marked flattening or scarring The lateral views simply exaggerate some of the points brought out in the antero-posterior description Exostoses are somewhat more prominent

Feet Right Changes are very slight in the bones of the feet Some enlargement of the ends The ends show slight periosteal swellings Some disproportion in length of the metatarsal bones Os calcis also shows slight periosteal and osteal changes The left foot is more affected than the right The greatest changes are seen in the os calcis, and in the third metatarsal The os calcis shows rather prominent exostoses, some transparency of the bone and definite penciling, also lack of development in the bones as a whole The third metatarsal is much shorter than the others The shortening is approximately 15 cm greater than in the other metatarsal bones Large exostoses are seen at the distal end

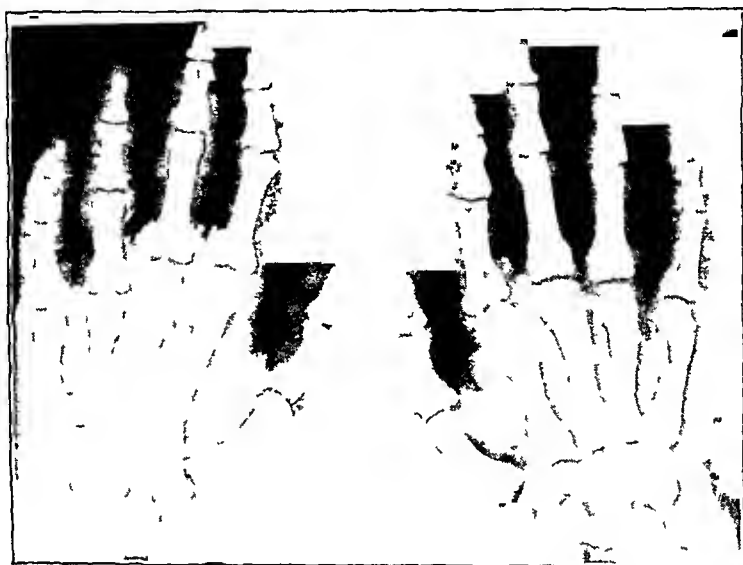


Fig 12—Case 2, E D Disproportion in length of metacarpals

Carpals Small, within normal limits

Metacarpals Right hand Very short, rather broad, especially proximal fourth and distal third The usual differences in length between the second, third, fourth and fifth metacarpals are lacking The longest metacarpal is 48 cm and the shortest is 43 cm The first metacarpal, however, is 32 cm

Left Hand Here the differences in length are well marked The bones are longer, contrast greater and the width not as marked as in the right hand The second metacarpal is 58 cm The fifth metacarpal is 35 cm Some exostoses are evident on the second fourth and fifth on the right, and on the third, fourth and fifth on the left These growths are all at the distal end approximately 15 cm to 1 cm from the end The ends of the bone both proximal and distal are quite porous The cortex is solid, well formed (Fig 12)

Phalanges Show nothing unusual except for some increase in width of the proximal head and an exostosis on the fourth finger proximal phalanx 5 cm from proximal end Joint spaces are clear

CASE 3—C G, male, American, born in Connecticut, aged 16, single occupation tool maker, entered hospital June 24, 1917

Diagnosis—Genu valgum Osteochondromata

*History*—All of his life patient has noticed lumps on various bones of body which have grown in the last six years. During the past few years patient has noticed that the right knee was becoming badly "knocked." Lumps are not painful.

*Past History*—Scarlet fever at 4, no other sickness.

*Family History*—Father and mother living and well, sister 3, living and well. No other members of family have any of these lumps.

*Physical Examination*—Patient is a well developed and nourished boy. Skin good color. Head no masses or tender points on scalp. Ears negative. Nose negative. Eyes pupils round, equal. React to light. Conjunctivae good color. Sclerae clear. Mouth teeth in good condition. Tongue clear.

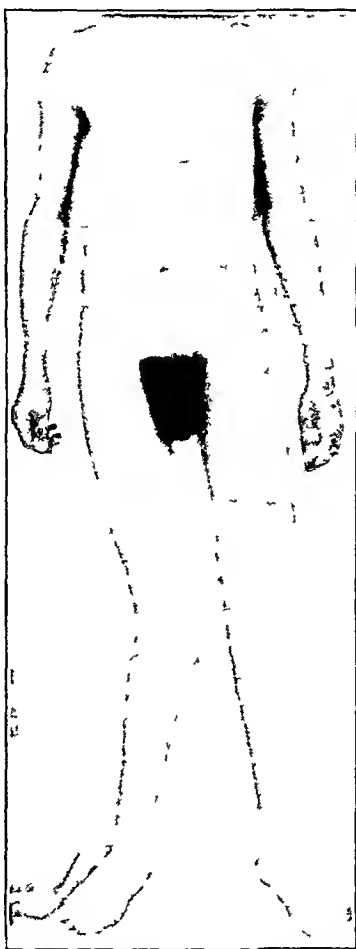


Fig 13—Case 3, C G. Disproportion in length of thorax to lower extremities and marked curvature of right leg.

Pharynx tonsils buried. Small white patch on right tonsil. No tumors about facial bones. Neck negative. Thorax no tumors of ribs. Abdomen normal, no masses or tender points. Liver and spleen not enlarged. Genitalia negative. Spine and pelvis free from tumors.

*Extremities* Scapulae and humeri free from nodules. Right forearm the ulna is bowed backward, especially near its upper end (Fig 13). There is a small cone shaped nodule near styloid process about 3 cm in diameter. Near distal end, anterior surface of radius, is a nodule about 5 mm in diameter. On dorsal surface of second, and third metacarpal bones, close to phalangeal joints is a small nodule only about 3 mm in diameter. None on fingers except nodule second phalanx, fourth finger, close to first phalangeal

joint Small nodule dorsal surface inner border first phalanx little finger near proximal end Nodule first phalanx, fourth finger near proximal end Nodule on outer surface of thumb about half way between joints The nodules on fingers are only a few millimeters in diameter

**Left Forearm and Hand** Similar bowing of left ulna though not so marked Nodule on posterior surface of ulna 2 mm in diameter and 3 cm from tip of styloid process On posterior surface of radius, close to inner border and 2 cm from articular surface, is a very small nodule On anterior surface of radius 2.5 cm from lower end is a nodule 1 cm in diameter There is a small nodule on dorsal surface of second phalanx of middle finger close to first phalangeal joint Small nodule on dorsal surface of first phalanx of index finger, about half way between joints Small nodule on fourth finger, dorsal surface, close to metacarpal phalangeal joint Small nodule on inner side dorsal surface of first phalanx little finger close to metacarpal phalangeal joint

**Right Thigh** In lower third outer surface of left femur is an irregular nodule (Fig 14), 7 by 5 cm On inner surface of femur just above condyle is a tumor 5 by 2 cm These tumors are all firmly attached to bone, are very hard, not tender

**Right Leg** On inner side of tibia is an irregular mass 8 by 4 cm, reaching to within 3 cm of upper end (Fig 14) Small nodule on outer surface of fibula 5 cm from upper end There is a group of nodules of varying size, from 2 mm to 1 cm in diameter, just above malleolus Similar group just above external malleolus

**Right Foot** No nodules The third toe is much smaller than normal (Fig 14)

**Left Thigh** There is a nodule on anterior surface of thigh 1.5 cm in diameter just above upper end of patella On outer surface is an irregular mass 5 by 3.5 cm beginning 5 cm from lower end of femur (Fig 14)

**Left Leg** Small nodule on outer surface of fibula 5 cm from upper end Two nodules just above external malleolus On inner surface of tibia close to upper end is an irregular group of nodules 9 by 5 cm Group of nodules just above internal malleolus (Fig 14) None on bones of feet

There is marked genu valgum of right knee (Fig 14)

**Blood Examination**—Leishman's Stain Ward IE, 7/30/17 Hemoglobin, 83 per cent, leukocytes, 5,760, polymorphonuclears, 180, 60 per cent, lymphocytes, 88, 29 per cent, transitionals, 22, 73 per cent, eosinophils, 2, 0.7 per cent, basophils, 1, 0.3 per cent, myelocytes, 2, 0.7 per cent, neutrophils, 2, 0.7 per cent, pathologic lymphocytes, 3, 1 per cent, total, 300, 99.7 per cent Red blood cells (1) some slight anisocytosis, (2) no poikilocytosis, (3) no nucleated red or basophilic cells, (4) platelets apparently normal in number

**Urine Examination**—June 25, 1917 specific gravity, 1.027 Otherwise negative

**Roentgenographic Examination**—Skull Diameters appear to be within normal limits Shape and general proportions of the skull as compared with the face and jaw bones within normal limits Tables are thin The sutures are not evident There is no evidence of fontanelles and the circulatory depressions are fairly discernible Sinuses are very large and transparent The sella turcica is within normal limits The maxillary sinus is very large and irregular in outline There is a small exostosis at the anterior nasal spine of the superior maxilla bone The mandible is well formed Shows an unerupted impacted molar The bones forming the orbit are very irregular in outline

**Vertebral Column** Cervical region vertebrae are small, delicately formed but within normal limits The dorsal vertebrae are also within normal limits There is a definite exostosis of the sacral region posterior and left lateral portions

**Ribs** Thorax is very narrow and long The ribs are very thin, poorly developed, narrow in width and show considerable bowing Downward angles



are increased and there is great disproportion in the width of the anterior rib spaces posteriorly and anteriorly There is much increase in width of the anterior ends and definite exostosis occurs on the right fourth rib and on the left second rib front

Clavicles Right shows slight bowing The left is straight Length of left clavicle is approximately 30.5 cm, right 14 cm Right shows the greatest changes, ends are much increased in width and the distal end shows a definite exostosis with considerable transparency and penciling of the bone There is periosteal thickening of both bones

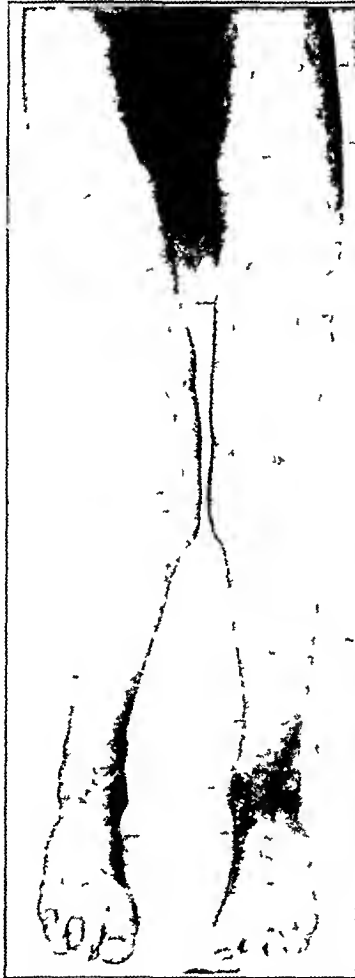


Fig 14—Case 3, C G On outer side of both femurs and inner side of both tibiae above and below are small nodules The middle toe on the right foot is much smaller in proportion than the other toes

Scapulae Are small, but the acromion processes are very large They are increased in width, transparent and show penciling The ends are irregular Scapulae outline is slightly irregular and there are definite exostoses occurring on the vertebral margin and just below the glenoid fossae on the left

Pelvis For the length of the femur, the pelvis is small, irregular in shape and with irregular surface outline There are numerous exostoses and growths on the iliae, also on the os pubis Os pubis is considerably deformed, increased in width and the symphysis pubis is increased in width also Pelvic cavity is decreased in size, although fairly symmetrical It is very difficult to determine the sacro-iliac synchondrosis on account of its extreme irregularity The os ischia are also bowed and deformed

**Radius and Ulna** Only the lower third of these bones was obtained. There is evident bowing and the ulna is shorter than the radius. The lower end of the ulna does not approximate the carpal bones within 1 cm. Ends of both bones are increased in width and there are definite exostoses just proximal to the epiphyseal line, and also a very large exostosis on the right radius 5 cm above the lower end. Most of these exostoses appear to be a definite part of the bones themselves. A good deal of penciling and transparency may be seen at the lower ends of the radius and ulna, and part of the epiphyseal line is evident. The styloid processes are rounded and shortened. Joint space is clear.

**Humerus** Only a small portion of the humerus shows. Approximate length of the left is 30 cm, right not obtained. Width of the upper half apparently increased and there are definite exostoses visible at the inner border on the right 6 cm from the epiphyseal line, and on the left 12 cm from the upper epiphyseal line. The epiphyseal line is evident and the epiphysis somewhat flattened, enlarged, transparent and with typical penciling.



Fig 15—Case 3, C G Enormous bony growths on lower ends of the femurs

**Femora** Approximate length of the right and left femur is 50 cm. Bones are affected from the head for a distance of approximately 13 cm and the ends for approximately 15 cm. The bones are equally affected. There is marked disproportion between head, neck and shaft. Neck is enormously widened but the whole upper end as well as the lower is extremely massive and club-like. The greatest width of the right is 8 cm above and 9 cm below. The left is 8.5 cm above and 10 cm below. The shaft (right) is 2.5 cm and the left is 3.3 cm. No definite exostoses, although the increased growth gives an irregular outline to the whole bone. The lower ends, however, show enormous stalactite growths one of which shows a beautiful cauliflower process at its terminal end (Fig 15). This particular growth is some 9 cm long and its greatest width is 2.5 cm. The bone is not particularly transparent. Longitudinal lines, however, are evident, although somewhat dense. The epiphyseal lines are also evident but are irregular, not sharply outlined in form, shape or outline. There are no growths, masses or bone changes. The joint spaces are clear (Fig 16).

**Tibiae and Fibulae** The changes here are remarkable. The ends of the bones are immense, with very irregularly formed exostoses, stalactite processes presenting a striking appearance (Fig 16). The length of the right tibia is approximately 39.5 cm, of the left 39 cm. Right fibula somewhat difficult

to determine on account of the growths, the right is approximately 36 cm in length and the left 36.5 cm. The width of the bones is impossible to determine on account of the fusing of the fibula with the tibia (Fig 17). The total width of the two bones upper end, right, is approximately 10 cm, lower end 10 cm, left approximately 11 and 6.5 cm. Right middle shaft of tibia 2.5 cm, left 3 cm. Right fibula 1.3 cm, left 1.3 cm. Except for 19 cm of negative bone in the shafts of both tibiae and fibulae, the rest is definitely affected. The shafts, however, show periosteal thickening. There are enormous coarsely formed exostotic growths. The bone itself (ends) shows heavy longitudinal lines, not very transparent. Epiphyseal lines are irregular and barely discernible. The heads of the tibiae show squaring, flattening and some widening (Fig 16). Joint spaces are apparently clear. The lateral views add nothing to the picture except the transparency is somewhat more apparent and in irregular and more or less circumscribed area. Some of the growths are continuous with the bone proper and others apparently have arisen from the cortex (Fig 18).

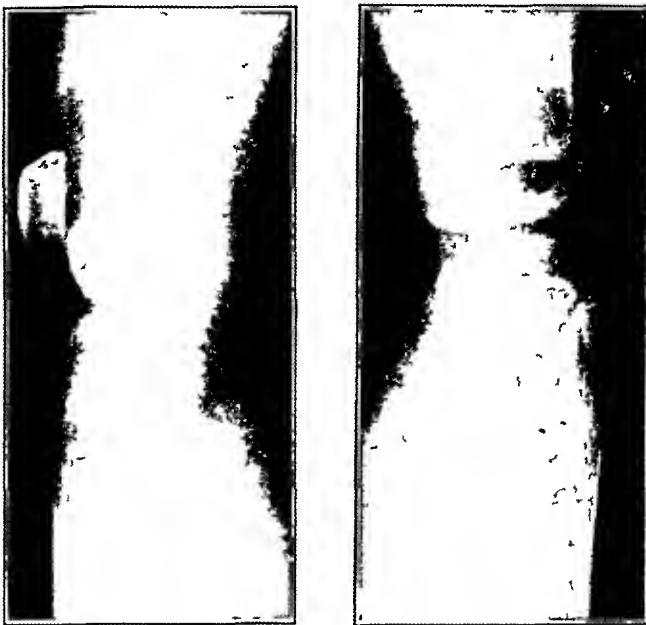


Fig 16—Case 3, C G Femurs, tibiae and fibulae showing growths on diaphysis and epiphysis

**Carpals** RIGHT except for some transparency and penciling of the bones and slightly irregular form, the bones are negative.

**Metacarpals** They differ in length and are disproportionate. The longest bone on the right is the third metacarpal which is 6 cm and the shortest is the first metacarpal which is 4.3 cm. The second measures 5.7 cm, fourth 5.6 cm and the fifth 5 cm. The proximal head shows the greatest widening, while both ends show transparency and irregular form with slight exostoses on the second and fifth bones. The distal epiphyseal lines are very evident as also the proximal epiphyseal line of the first metacarpal. There are also periosteal changes in shafts of the second and fifth metacarpals.

In the left hand the longest bone is the second metacarpal which measures 6.5 cm, while the first and fifth are equal in length, being 5.4 cm. The third is 6 cm and the fourth is 5.5 cm. The changes are similar to those in the other hand, the only exception being the third metacarpal which is most affected. The interesting point in the metacarpals of both hands is that the distal epiphyses show these changes. The greatest changes are seen on the ends of the bone 1 cm and less from the epiphyseal line.



Fig 17—Case 3, C G Disproportion in development of both tibiae and considerable bowing of the right tibia



Fig 18—Case 3, C G Lateral view of lower end of tibia showing outline of growth continuous with bone growth

**Phalanges** Also show disproportion in length. The right hand shows the proximal phalanx of the second, third and fourth digits to be of the same length while the left shows the second to be shorter than the third and fourth. The flaring of the shafts and periosteal changes and the increase in width with slight exostoses is the same as described in the other cases. The epiphyseal lines are sharply demarcated and well discernible. There are definite exostoses on several of the phalangeal bones. The joint spaces are clear. There are no marked deformities.

**Feet** Lateral views only. These show the greatest changes in the metatarsals which are bowed, irregular in outline, enormously increased in width at the proximal and distal ends with definite exostoses on several of the bones. There is also some transparency and pencilling, mostly of the proximal por-

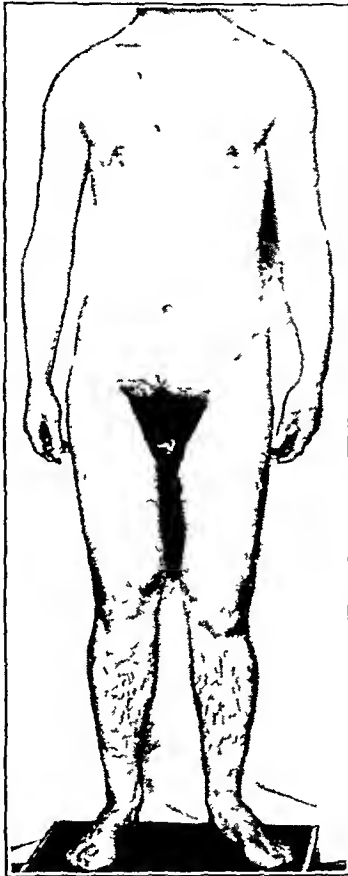


Fig 19—Case 4, R W H. The disproportionate shortness of the lower legs is well shown.

tions. The tarsal bones show beautiful pencilling and an increased transparency. The os calcis is large and well developed, whereas the astragalus is well developed, small. The growths are exaggerated and the portions are disproportionate in size. There are also periosteal changes. No definite exostoses. The joint spaces are sharply outlined and perfectly clear.

**CASE 4**—R W H, born in South Carolina, age 31, male, single, occupation till 19 on farm and then clerk and bookkeeper. Lived in South Carolina all his life. Average weight, about 114 pounds. Examined, June, 1918 (Fig 19).

**Family History**—Grandmother, father's side, died of old age, 69 years, grandmother, mother's side, died at 33, cause unknown, grandfather, father's side, killed in Civil War, grandfather, mother's side, died of old age, 79 years.

Mother died at 38 from pneumonia. Father living at 62 in good health. Tall. On mother's side all of good size. She, however, was quite short in comparison to others. Two uncles, both healthy, but younger of two is similar in stature to patient. Four aunts, nothing abnormal. One brother alive and well, 70½ inches in height. Three sisters alive and well. One sister died of tuberculosis at 18. Four half brothers born after second marriage of father, all alive and well with exception of one who is similar to patient in stature, but very strong. One half brother died probably of typhoid fever. Three half sisters all healthy. Seven nieces all alive and well, three nephews alive, two are well, one has peculiar throat trouble, otherwise well. One nephew died in childhood, cause unknown. All normal in size. Mother and father were third cousins. Second marriage no relationship at all. Family diseases—no cancer, no heart disease, no "rheumatism," no pellagra, no hookworm. Tuberculosis in one sister, an aunt and three of her children.

*Past History*—Breast-fed till 1½ years old, then usual table diet. (Breakfast: Meat, corn mush, butter and syrup, flourbread. Noon: Vegetables, milk, bread and butter, pie, corn bread. Supper: Rarely meat, milk, butter, corn bread and butter, fruits and milk. Corn bread was quite commonly used.) Diseases: Measles, whooping cough, mumps, malaria (?). Mildest kind of attacks. No "stomach trouble" in childhood. In 1912 a nervous breakdown with gastric disturbances. Pain in epigastrium after meals and between meals. Pain was general and not related to meals, occasionally when without meals. Never vomited. No bowel disturbances. Always able to work and gained in weight during his illness. Venereal History: Gonorrhea in 1916, duration one year, treated and cured. Syphilis denied. No history of secondaries.

*Present History*—At 6 years father noticed enlargement on inside of right ankle. Was treated with iodine locally. No diagnosis made. Within two years the other ankle showed enlargement. There was no pain or difficulty in walking. From time to time, until 10 years of age these lumps were discovered all over the body, especially under left arm, in axilla, and on ribs. Since that time, between the ages of 10 and 15 they appeared on lower extremities and after an injury to left hip on that region. During this time fell on coccyx and a mass developed there, this, however, was somewhat softer than the others. Met with no other accidents, never had any fractures. Last one noticed was on the outer side of the right thigh, at age of 23, following a fall two years before, at which time he had distinct ecchymoses. Never penetrated skin. Has noticed certain ones disappear under arm, on left wrist and little one on thumb. One on wrist disappeared five years after first noticed, when he was 14 years old. Size was about that of a half-dollar and elevated skin about a quarter of an inch. Chief complaint: Limitation of motion, lower limbs only. Cannot bend and reach feet normally and is handicapped on hikes and in calisthenics. Otherwise no discomfort. Urine and blood examination of no interest.

*Röntgenographic Examination*—Skull: Diameters within normal limits. The proportions of the face are comparable to those of the skull. Teeth show normal dentition. Sinuses within normal limits. The bones are of normal density except for the mala and zygoma which are larger and heavier, slightly more irregular than normal. Tables of the skull, posterior half show increased width, are denser and the internal and external surfaces show some irregularity. Sella turcica is fairly large, within normal limits. The sutures, circulatory depressions and intercranial density within normal limits.

*Vertebral Column*: Cervical vertebrae irregular in shape and form. Surface is also somewhat irregular. There are no definite exostoses. The dorsal portion shows a definite double lateral curvature. Vertebrae, are well formed.

*Ribs*: The ribs are considerably more bowed on the right than on the left. Downward angle of both sides increased. Rib spaces are very narrow. Thorax is definitely asymmetrical. Anterior ends are increased in width and are somewhat irregular.

**Clavicles** Show considerable bowing and are enormously increased in width at the ends. The right measures approximately 15 cm in length. The proximal end is 3.5 cm wide, distal end is 3 cm wide. Middle of the shaft is only 1.5 cm wide. The bones are affected for approximately 5 cm from the ends leaving approximately 5 cm unaffected. The left is also 15 cm in length, 2.5 cm wide proximal end, 1.8 cm distal end, middle of shaft is 1.5 cm. Left consequently is not as much affected as the right. Definite exostoses and same changes described in the other bones are seen here.

**Scapulae** Are decidedly small if compared with the acromion process and the humerus. Angles are increased, surfaces are irregular. Glenoid fossae are shallow and small. Acromion shows increased length and width—is also transparent, with considerable penciling. The distal surface is slightly irregular. The acromion clavicular junction is increased in width and the end of the clavicle does not fit as closely as in the normal. This is usually due to changes in the clavicle.

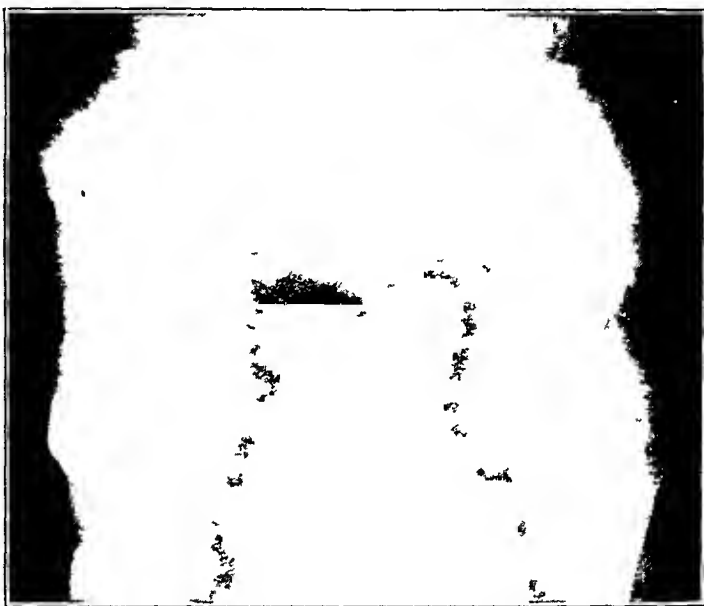


Fig 20—Case 4, R W H Asymmetry of pelvis and large head, neck and trochanters of the femur

**Pelvis** Within normal limits as to general size, proportion and shape, except for changes in the os pubis, where the bones are somewhat irregular in outline and shape and show definite exostoses. They are increased in width and are well contrasted to the os ischii. Definite exostoses left ilium mid-portion, superior posterior surface. Outlines of the bones in general are irregular. Bones are not transparent. There is a slight asymmetry of the pelvis as a whole (Fig 20).

**Radius and Ulnae** Bones of both forearms are curved (Fig 21). Surfaces are irregular. The ends of the bones are considerably more porous than usually. The cortex is not visible in several areas. The middle of the shafts shows the medullary canal to be considerably occluded. In the right the radius from the head to the tip of the styloid process is 23.4 cm and on the left is 23.7 cm. Right ulna from the tip of the olecranon process to the tip of the styloid process is 23.9 cm. On the left, the ulna is 22.9 cm. The width of the shaft of the radius, right is 1.6 cm and left 1.7 cm. The width of the ulna, right, is 2 cm and left 1.5 cm. Greatest changes are seen at the ends of the bones approximately 7 cm from the lower end of the right radius and approximately 6.5 cm from the lower end of the left. The proximal ends of

the ulna, however, show the greatest changes. The heads and the coronoid processes are increased in width, are very porous and irregular in outline. The epiphyseal lines are practically indiscernible. The epiphysis and diaphysis appear as one bone. There are definite exostoses, the largest being on the right 5 to 7.5 cm from the lower end adjoining the ulna. The shape of the ends of the bone is considerably distorted, blunted and rounded. Joint spaces are clear.

**Femora.** Right. Length of the femur approximately 15 cm. Width, right upper, approximately 9.5 cm, lower 9 cm—if including the exostoses 10.5 cm, middle of shaft 2.5 cm. Left. Length of left femur approximately 19 cm. Width, left upper 9.5 cm, left lower 9.5 cm, middle of shaft 2.5 cm.

The bones are affected for approximately all but 18 cm of the shaft. Ends of the bones appear as massive clubs, irregular in form and outline, with definite large round and stalactitelike processes (Fig. 22). Some of these have



Fig. 21—Case 4, R. W. H. Considerable bowing of the radius and ulna, disproportionate growth in length, rounded styloid and exostoses.

undergone complete ossification. There is great lack of proportion between the neck, head and shaft. The epiphyseal lines are not discernible. The lower ends show no cortex and the growths are apparently continuous with the growth of the bone and show distinct longitudinal penciling with transparency. The shape of the lower epiphysis is within normal limits and the joint space is clear.

**Humeri.** Right is approximately 35 cm long, left is 33 cm long. Right does not show as much change as the left. The head is 6 cm in width as compared with 3 cm for the middle of the shaft. This last measurement, however, is increased because of a definite round periosteal thickening. The cortex is visible throughout and only slight changes are seen in the middle



and in the inner upper ends approximately 10 cm from the head Epiphyseal line is fairly well seen The lower end of the bone shows very slight changes, some increase in width, some periosteal change and decided transparency Right no greater, however, than the left Left Head is 57 cm wide and 10 cm below this it is 45 cm wide Bone is affected for a distance of 16 cm Definite exostoses with marked cortex, medullary and periosteal changes are seen The lower end is practically unaffected Epiphyseal line not determined In both cases there is lack of contrast between the surface, neck and the shaft Joint spaces are clear

**Tibiae and Fibulae** The most striking changes are seen in the tibiae and fibulae Ends are fused together In the case of the left lower tibia and fibula which appear as one bone, middle of fibula is almost as wide as the tibia (Fig 23), being 17 cm as compared to 25 cm on the right and the



Fig 22—Case 4, R W H Enormous growths of different types on both the upper and lower extremities of the femur

left 17 cm as compared to 23 cm There is no division line Longitudinal lines are transparent and continuous throughout Right tibia is 36 cm in length, fibula is 33 cm in length (Fig 24) Left tibia 34 cm in length and the fibula 31 cm Greatest width of right tibia is approximately 8 cm above and 5 cm below and 25 cm in middle of shaft The fibula cannot be determined on account of its enormous growth Left tibia is approximately 7 cm wide above, but cannot be determined below The total width of the tibia and fibula is 55 cm Practically the entire diaphysis is affected except for an area not greater than 10 cm on the right and 8.5 cm on the left Fibula appears affected throughout There is marked transparency of the ends

Throughout the whole bone beautiful longitudinal penciling is seen. The epiphyseal line is not discernible. The upper epiphyses of the tibia are flattened, square and somewhat irregular in shape.

**Carpals**—There is considerable disproportion between the various carpal bones of both hands. Capitate is very large and the lesser multangulum is very small. The greater multangulum appears to be fused with the lesser multangulum. This is also true of the capitate with the hamate bones. The trapeziform bone on the right shows a definite exostosis (Fig 25).



Fig 23—Case 4, R W H. Lateral view of the tibiae and fibulae showing distribution and types of new growths.

**Metacarpals**—Show a marked disproportion in size in both hands. The right longest bone is the third metacarpal which measures 6 cm and the shortest is the fifth which measures 4.5 cm. The first and fourth measure 4.6 cm. On the left the longest bone is the second metacarpal which measures 6.7 cm and the shortest is the first metacarpal which measures 4.2 cm. The fifth is 5 cm long, the fourth, 5.5 cm and the third, 6.3 cm. Heads of both proximal and distal are enlarged and show considerable porosity. There is, however, no deformity of the metacarpals on the right but on the left the second, fourth and fifth are deformed. Exostoses appear approximately 2 cm from the distal end (Fig 25).



Fig 24—Case 4, R W H Anteroposterior view of tibiae and fibulae showing growths on both bones and disproportionate development

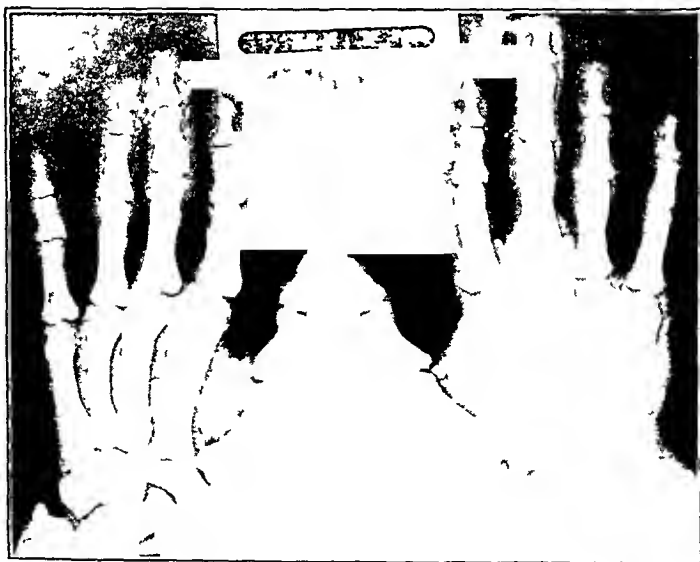


Fig 25—Case 4, R W H Variation in length and size of carpals and metacarpals deformity of wrist

**Phalanges** There are considerable changes in the phalanges of both hands. For the most part, the bones are porous, the cortex well outlined, the bones increased in width and the surfaces considerably irregular. There are also definite small exostoses seen on eight of the bones in the different fingers (Fig 25). Wherever there is an exostosis the porosity of the heads apparently continues with the exostosis.

**Feet** **Right** Changes in the metatarsals are as marked as those seen in the metacarpals. The second metatarsal is only 5 cm in length, the first being 6.3 cm, the third, 7 cm, the fourth, 6.5 cm, and the fifth 6 cm. The left metatarsals do not show the same changes. The ends of the bones are increased in width and the epiphyseal lines are not evident. Marked transparency and beautifully pencilled longitudinal lines are seen and definite small exostoses occur. The same changes are noticeable in all of the phalanges.

The tarsal bones, except for their greater transparency and penciling, show very slight changes. Joint spaces are clear.

### DISCUSSION

From a study of these four cases it is evident that the flat bones, that is, the scapulae, iliae, ribs and even the skull bones, are frequently affected and to quite an extent. The long bones, although markedly affected in most cases, may, in some cases, present very little change. This is quite noticeable in the humerus. In general, the femur, tibia and ulna bones show the greatest growth changes and, on the other hand, the vertebrae and facial bones show the least, often no changes at all.

TABLE 1—THE LENGTH OF METACARPAL BONES. THE MEASUREMENTS IN FOUR CASES OF EXOSTOSIS ARE COMPARED WITH THE AVERAGE IN TWENTY ADULT CASES

	Right Hand					Left Hand				
	1	2	3	4	5	1	2	3	4	5
Normal	4.5	6.7	6.7	7.4	7.5	4.9	6.5	6.7	6.0	5.5
Case R B	4.0	6.2	5.7	5.8	5.0	4.2	6.5	6.2	5.5	5.4
Case F D	3.2	4.7	4.9	4.5	4.4	3.6	5.8	5.2	3.9	3.5
Case C G	4.3	5.7	6.0	5.6	5.0	5.4	6.5	6.0	5.5	5.4
Case R W H	3.6	5.5	6.0	4.6	4.5	4.2	6.7	6.3	5.5	5.0

The changes in the bones can best be studied under two heads. Those affecting growth, that is, form, length and size, with relative changes in periosteum, osteum and medullary canal, and those showing proliferative and inflammatory-like changes.

Growth retardation can best be seen in the metacarpal bones. We have in the normal fairly definite lengths and comparative sizes for the different metacarpal bones and these run fairly true (Table 1). In our cases there is marked variance in the length, form and size of the different metacarpals in the single hand and most strikingly so when the two hands are compared. These changes must necessarily have begun very early in life to be of so pronounced a type at present. They are not retrogressive processes on the part of some bones and

progressive processes on the part of other bones. The carpal bones show fairly marked changes but mostly in size and form. It is difficult to judge whether such changes may not be due partly to pressure between the long bones of the forearm and fingers, resulting on the one hand in definite excessive growth and on the other in retardation of growth.

Similar changes are seen in the scapulae, the pelvic bones, the metatarsals and to some extent in the tarsal bones. In the scapulae the disproportion between the body of the bone and the acromion process is very noticeable, the acromion process is exceedingly large, the body and the glenoid process small. When the head of the humerus is enlarged, as it invariably is, the smallness of the glenoid cup is striking. Changes in the growth of the bones are also seen in the ulna, radius and fibula. These changes are of a different type, however, and are not so consistently present. In the case of the radius and ulna one of the most interesting points is the absence very often of the styloid process. This gives evidence, therefore, of the very early changes that occur in this disease.

Changes in growth may frequently involve only part of a bone or one bone in a group, such as is seen in the femur where the head, neck and trochanters are affected and the shaft and condyles are apparently unaffected or in the case of the wrist bones where the os magnum may be markedly large in comparison with the other carpal bones, or, again, in the case of the phalanges where the proximal or middle phalanx may be unusually short as compared with the apparently normal length of the other two phalangeal bones.

In the majority of bones the normal length has been reached, and growth has been retarded only in respect to their size. The ribs, for instance, are abnormally delicate and symmetrical, but their length compares favorably with the normal. The radius in some portions may show a very small diameter as compared with the other bones of the skeleton or with the normal, but this is quite a different process. In the case of the ribs there are no marked growths, no enlargements or compensation in growth in one part as compared with another, but, in the case of the radius it is conceivable that the lack of growth in one part may be due to the excessive growth in another. It is suggested, therefore, that when the length of the bones is not interfered with, there may be one of two causes, either the epiphyses are unaffected in early life or the growth, such as is seen in the heads and neck of the femur, occurs later in life when the growth in length of bone has been reached. If this is conceded, then there are dissimilar processes going on in different bones either at the same time or at different periods of growth.

A study of the location or site of the growths or processes demonstrates two main facts, that they occur both distal and proximal to the epiphyseal line and that the two processes may be entirely dissimilar. The growths or enlargements at the epiphyses may be extended downward so as to be continuous with the process on the diaphysis or they may be separated. It is frequently difficult to determine to just what point the process extends as the changes from the gross to the minor are so gradual and often very variable. For instance, the growth at the epiphyses may be of a large, diffuse proliferative type affecting all portions of the bone and just below this may occur changes in cortex and periosteum within regular bounds and finally lower down there may be a purely periosteal reaction, similar to any inflammatory periosteal reaction. Frequently, the epiphysis is affected, showing a fairly intact epiphyseal line with no change in the ends of the diaphysis, but a definite, more or less localized periosteal and slight osteal growth is seen on the diaphysis proper, probably at its middle. This last point suggests another process, perhaps not directly and primarily related to the epiphyseal processes.

A study of the growths demonstrates, further, the differences alluded to above. For the sake of a clearer understanding of the matter, these are divided into three groups.

a *The Epiphyseal Changes*—The epiphyseal changes are mainly enlargements and distortions of form and vary considerably in the different bones. In the femur I have seen no growths on the head, but the great trochanters show frequent large irregularities. The femur shaft from just below the trochanters to the articular surface is so large and irregular in form as to bear little or no resemblance to the normal femur. The neck is double the diameter of the head, instead of presenting the usual constriction between head and trochanter. The cancellous lamellae do not run in well formed continuous lines, but in criss-cross directions, and in interrupted lines. These lines may be heavier and denser than the normal or, if much absorption has taken place, then in delicate pencilled lines. The condyles of the femur are enlarged, rather hypertrophied, the form becomes more or less square, the surfaces flattened. The longitudinal diameter is increased to twice the normal and the interlamellae spaces are much increased in size, consequently the bone is more transparent than the normal. I have seen no growths on the condyles, although growths occur just at the epiphyseal line. The head of the tibia shows the same changes as the condylar end of the femur. The fibula head and the acromial process of the scapula are distinct exceptions. Here definite growths occur and these are epiphyseal in origin. The vertebral border of the scapula also shows growth. The metacarpals, meta-

tarsals and the phalanges are also exceptions. The epiphyseal ends here are early affected, changes in form and outline with distinct growths developing before puberty.

Table 2 gives the dates at which ossification of the epiphyses and their union to the shafts of the bones become recognizable by means of roentgenography. It is for use in comparison with four cases of multiple cartilaginous exostosis.

TABLE 2—TIME OF RECOGNITION OF OSSIFICATION OF EPIPHYSES AND THEIR UNION WITH SHAFT BY MEANS OF ROENTGENOGRAPHY

	Normal		Cases			
	Time of Appearance of Epiphyses	Time of Union with Shaft	B, 22 Yrs	D, 16 Yrs	G, 16 Yrs	H, 31 Yrs
Clavicle	18th to 20th year	22d to 25th year	c	c	c	c
Humerus						
Head	3d to 4th month	20th to 25th year	c	dl	—	c
Great tuberosity	2d year		c	dl	—	c
Lesser tuberosity	3d year		c	?	—	c
Lower epiphysis		18th year				
Capitellum	End of 2d year		c	c	c	c
Trochlea	10th to 13th year		c	c	c	c
External epicondyle	12th year		c	?	c	c
Internal epicondyle	5th year		c	?	dl	c
Radius						
Head	5th to 6th year	16th to 19th year	c	c	dl	c
Lower epiphysis	2d to 3d year	17th year	c	dl	dl	ic
Ulna						
Olecranon	10th to 13th year	20th to 21st year	c	c	c	c
Lower epiphysis	5th to 7th year	20th to 24th year	c	dl	dl	c
Styloid process	4th year	20th to 24th year	c	c	c	c
Metacarpals						
Thumb (base)	7th to 8th year	16th to 20th year	c	c	dl	c
Other digits (heads)	4th to 6th year	16th to 20th year	c	c	dl	c
Phalanges	4th year	18th to 20th year	c	c	dl	c
Femur						
Upper epiphysis	Shortly after birth	18th to 22d year	c	c	dl	c
Great trochanter	4th to 5th year	18th to 22d year	c	e	dl	c
Lesser trochanter	13th to 14th year	17th to 22d year	e	c	e	c
Lower epiphysis	9th fetal month	22d to 24th year	c	c	dl	c
Patella	3d year		c	c	e	c
Tibia						
Upper epiphysis	9th fetal month	18th to 24th year	e	ic	dl	ic
Lower epiphysis	1st to 2d year	16th to 18th year	c	ic	dl	e
Tubercle (if separate)	12th to 13th year	18th to 24th year				c
Fibula						
Upper epiphysis	4th to 5th year	20th to 22d year	e		dl	c
Lower epiphysis	2d to 3d year	21st to 23d year	c	ic	dl	c
Metatarsals	3d to 8th year	16th to 19th year	c	c	dl	c
Phalanges	5th to 8th year	18th to 20th year	e	c	few	c
Epiphysis of os cileis	7th to 10th year	16th to 18th year	c	c	e	c

Explanation: c, complete, no evidence of epiphyseal line; ic, incomplete, line still evident; dl, definite epiphyseal space vacant.

The most striking epiphyseal changes, perhaps, are those of the fibula and acromion. In both these bones it is of importance to note that the bodies themselves suffer in length and size just as occurs in the metacarpal bones. In the case of the fibula early fusion with the tibia may play a part in retarding growth of the bone.

Changes therefore, occurring in the epiphysis of the bones may be metaplastic but under control, metabolic or may appear as unrestricted growths.

In studying epiphyseal changes, one of the most striking features is the early disappearance of the epiphyseal lines or space, but this is by no means constant, even in the bones of a single case (Table 2). Two of the patients were only 16 years of age, so it is presumed that ossification and union took place a year or more previously, judging from the density of the bones and the total absence of an epiphyseal line. This may be due to the growths either directly or indirectly by pressure, or it is even possible that if a longitudinal section were made through the epiphysis, traces of an epiphyseal line would still be seen. This fact, therefore, has an important bearing on the growth of the bone and would apply to the marked changes seen in the fibula and also the bones of the forearm. In the case of the tarsals, metacarpals and phalanges it can have little bearing, as retarding influences must have been present long before epiphyseal factors played a part.

b *Changes at the Diaphyseal Ends*—The greatest and most common changes occur at the ends of the shaft adjacent to the epiphysis. In the lower ends of the femurs and in both ends of the tibia the changes are most striking. They may encroach on the epiphysis (Fig 26), but they originate on the diaphysis. These growths affect the bone itself. The ends are enormously enlarged, irregular in shape and outline, giving rise to curiously shaped outgrowths, some stalactite in type, five and more centimeters in length and two and more in diameter. The terminal portions are often cauliflowerlike, with areas of irregular transparency, indicating incomplete cartilaginous ossification and other areas denser than the normal bone. They grow in all directions, mainly, however, longitudinal and parallel to the bone, suggesting progress in the direction of least resistance. It is also possible that muscular movement, since small areas of muscle attachment appear on the growth, may sufficiently irritate to excite further growth of these projections. They also apparently have a great tendency to deposit calcium. There is no base to these growths. The cancellous lamellae of the bone are often continuous with the growth. They apparently represent changes originally of the bone itself. Frequently, cortex and an inner canal of a different bone structure can be seen in the growth. The part of the diaphysis affected often shows no cortex, no medullary narrow canal and the bone structure apparently is much disorganized. These growths may interfere with joint movement, such as a growth on the tibia exerting such pressure on the fibula as to interfere with its development (Fig 26). The excessive bone growth of the diaphysis in one part may affect the growth of the bone in another part. Bowing of the shaft frequently seen, suggests unequal growth, as in the case of forearms or lower legs. These points suggest the very early changes that occur in the bones themselves.



c *Exostosis and Periosteal Growths*—In quite a number of bones two types of changes appear apart from what has already been described. One is a definite exostosis arising directly from the periosteum or osteum, that is, having at its base the normal cortex of the bone. These occur most commonly on the diaphysis, anywhere between the ends of the bone. In appearance they are not different from mechanical exostosis seen in many individuals. The other is rather a nodular swelling of the periosteum, organized to a certain extent, but to be differentiated from the cortex and also having as its base the

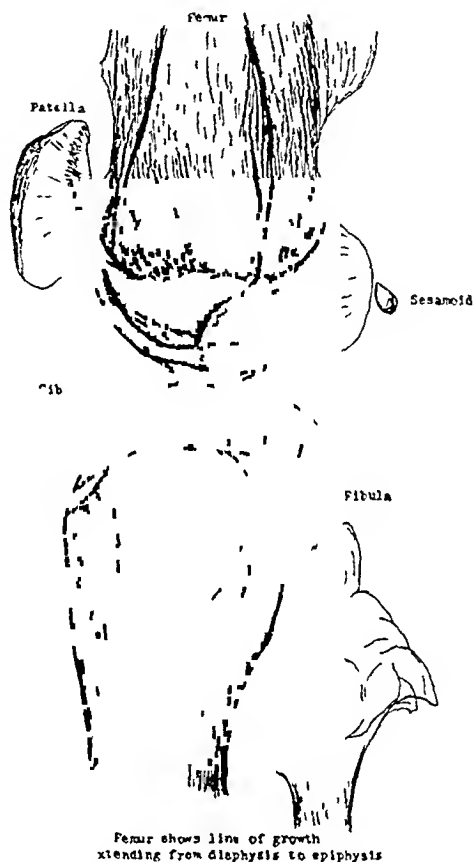


Fig 26—The ends of the bones are enormously enlarged, irregular in shape and outline, with curiously shaped growths. They originate in the diaphysis but encroach on the epiphysis.

cortex. The surface is not broken, is smooth, with an elevation of a centimeter or more, and three or more centimeters in diameter. They also occur on the diaphysis, frequently near the middle and on otherwise unaffected bone. They occur frequently, if not always, after an injury, may disappear gradually, and, on the other hand, may develop rapidly. The history in two of these cases gives proof of this, and in one case this was observed. These nodules may become completely ossified. It is suggested that this type of exostosis and these nodules have a common cause, for they are constantly associated. It further-

more suggests that the bone itself is sensitive to injury and sets up an inflammation, reacting in this manner

There is no evidence from the roentgenograms to show that these growths are anything but benign. No evidence is obtained that any

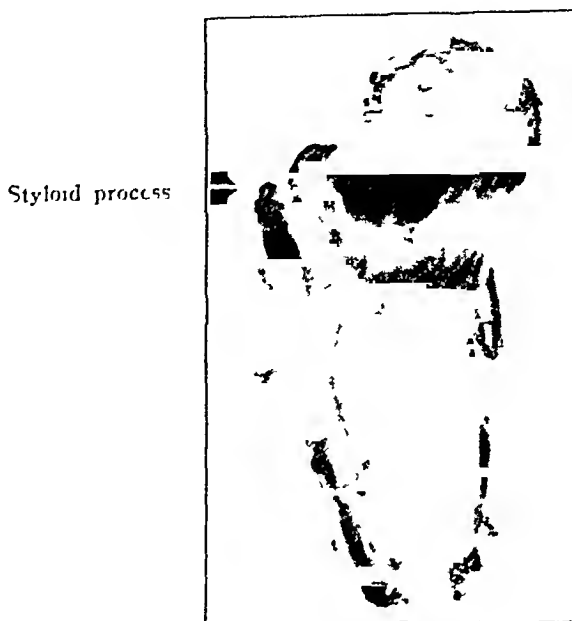


Fig 27—Pseudo-epiphysis produced by the process of exostosis, with cauliflowerlike cartilaginous surface and with processes for the insertion of muscles  $\times 1$

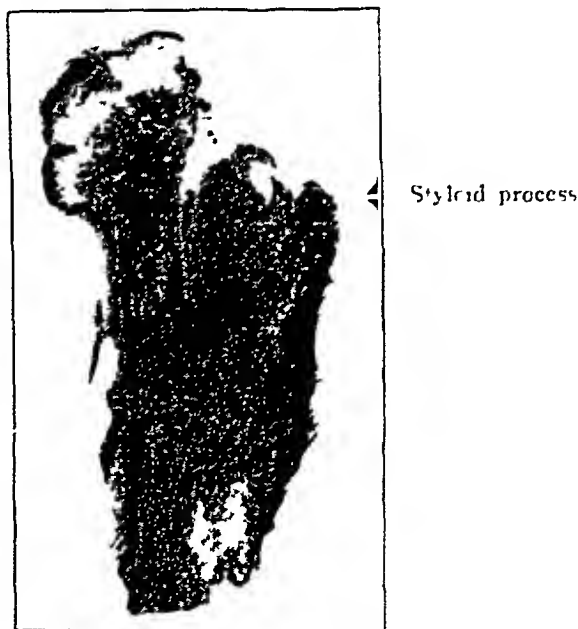


Fig 28—Longitudinal section of pseudo-epiphysis showing solid bone throughout, with an irregular cross line at the neck and spongy substance at the cartilaginous surface. There is no medullary canal  $\times 1$

degenerative changes occurred. These growths develop slowly in some cases and rapidly in others. In one case (G) the growth, exostosis, was removed. A drawing of this is shown (Figs 27 and 28), and the pathologic report is also included in this paper.

In many instances symmetrical changes are seen, that is, in distribution. But since the disease affects the epiphysis, ends of the diaphysis and diaphysis, and is a general skeletal systemic disease, some symmetry in distribution is to be expected. The growths vary, the position of the growths vary, their size, structure and development varies, and in this respect they are not symmetrical. In examining some of the growths in detail, one or two interesting points are brought out. In the case of G a very typical growth shows a cauliflowerlike end 2.5 by 3 cm. in size. The growth is about 10 cm. in total length and is situated 13 cm. from the lower end of the femur. The end is made up of numerous, small, semicircular areas of transparency much like a honey comb (Figs 29, 30 and 31). The surface outline is no greater in density than the internal structure, indicating cartilaginous nature and no peripheral bone salts deposit. In the case of B a similar type of growth is seen occurring on the inside of the shaft of the right femur. Here the growth, however, shows calcification with differentiation between cortex and canal. The peripheral outline is denser than the rest of the bone growth and its outline smooth. Comparing this growth with that of G there is a suggestion that differentiation in the growth occurs only when general growth has ceased. In the case of G we are dealing with an individual who has not reached maturity, as judged from the normal line of ossification, in the case of B with an individual who has. It is further suggested, that the processes are most active and form a part of general bone growths in youth, in no way controlled or restricted as occurs in normal bone growth, maturity alone restricting growth.

In the growth from patient G a fracture through the shaft of the growth occurred, 3 cm. from its base. No symptoms were present.

In the general roentgenographic description of the bones it will be noticed that the increased transparency and the penciling is a prevailing change. The question arises, therefore, whether these growths affect the structure and strength of the bones. Attention has been drawn to the early inhibition of growth, of bowing and general mechanical changes. On close examination of some of the bones that show bowing, it is found that this does not occur in the region of an unaffected shaft but in both the upper and lower ends of the diaphysis which, as already described, show bone changes. Do the growths or the general processes which give rise to them affect the bone? This I believe to be the case, and if the metabolic tables are studied the question will arise whether the increased elimination of salts can possibly come from the growths alone or are at the expense of the bones themselves. The metabolic disturbances and the growth processes have, then, a relation to one another. On the one hand, we have restricted bone growth, and on the other, excessive, uncontrolled bone growths.

in various forms. From this standpoint it is assumed, then, that metabolism was disturbed or imperfect very early in life, perhaps in utero. If attention is also drawn to the fact that these bone disturbances cease after maturity has been reached, the above assumption is even more acceptable (see results of metabolic studies).

Rickets is an analogous condition in the long bones, except that no growths occur and the hereditary factor is absent. It is a disease due to metabolic disturbances and results in very definite bone changes affecting growth.



Fig 29—Cross section of pseudo-epiphysis. The squared areas are enlarged in Figures 30 to 33.  $\times 15$

In multiple cartilaginous exostosis there is no association with any other disease so far as is known, and the only complications are those which arise or occur in the growths themselves, degenerative changes, malignancy or fractures and these are infrequent. Mechanical inconveniences due to the growths are not complications.

As has been pointed out by numerous investigators, the male is affected most commonly; the ratio is more or less three to one.

The last question is one of heredity. A careful study of the literature leaves no other conclusion but that it is an hereditary disease. From earliest times to the present day the literature on the subject presents very convincing evidence that hereditary factors play a part

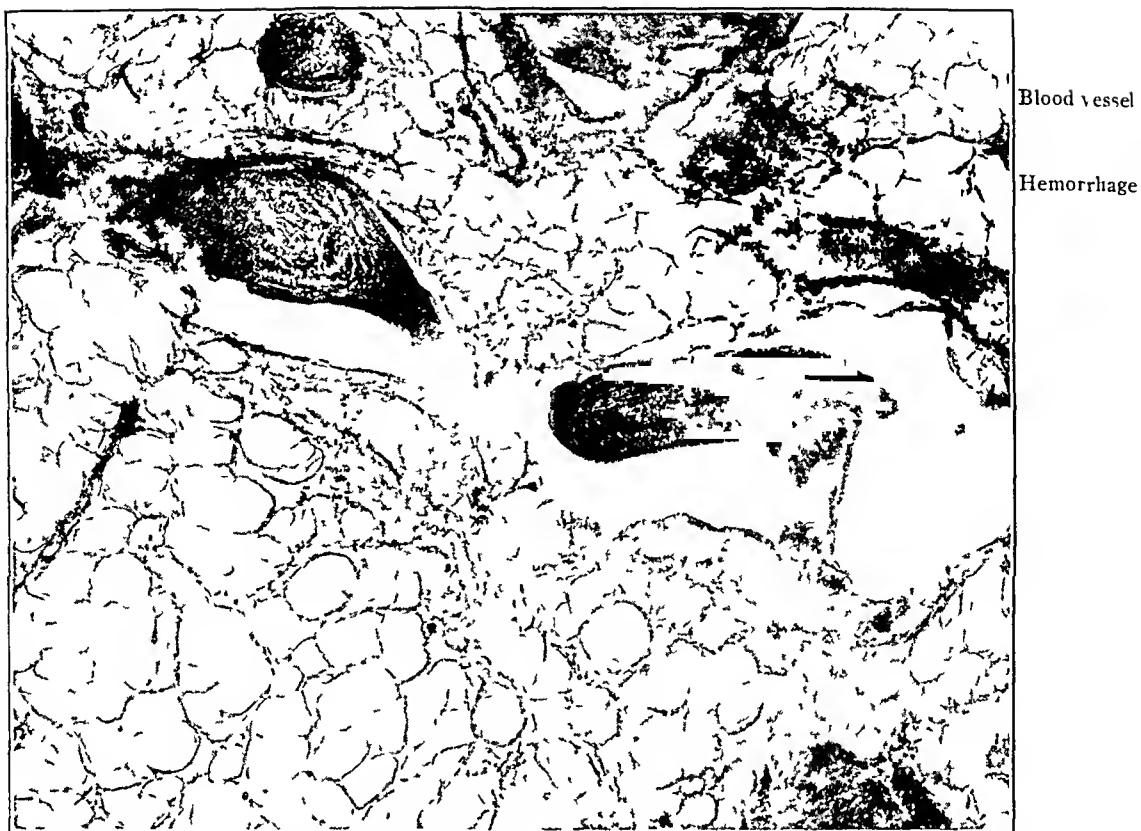


Fig 30—Bony spiculae surrounded by osteoplastic connective tissue  $\times 70$

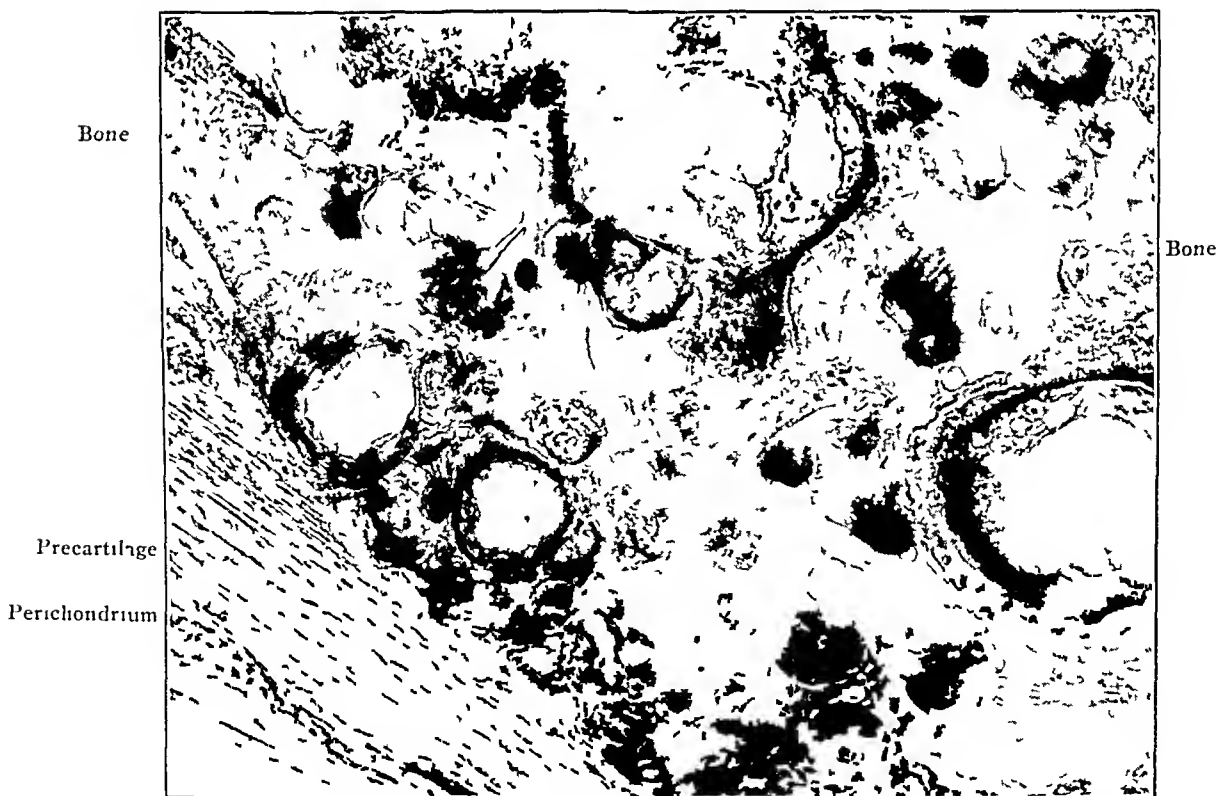


Fig 31—Precartilage with perichondrium in transition to bone  $\times 150$

It is hardly convincing that, because no evidence of the disease appears in the ancestors of a given patient, that hereditary factors should be ruled out, for it presumes that the disease is, therefore, one of remarkable individual selection. This paper, however, does not pretend to enter the discussion of the hereditary factors. That is a study by itself.

#### CALCIUM AND MAGNESIUM METABOLISM

Two patients, G and H, were studied. These patients were placed on a known diet low in calcium and magnesium for a definite period. Either calcium or magnesium was then added for a second period. Calcium intake was increased by the administration of milk. Magnesium was given in the form of citrate. By the procedure outlined it is apparent that the system was given a distinct task to perform. The manner in which this task was accomplished by the diseased system was checked up by comparison with normal subjects maintained under similar experimental conditions. Of these two cases, one had advanced to the stage where the abnormal processes had become stabilized (H). The other case (G) represented the active, less advanced stage of the disease.

#### RESULTS OF EXPERIMENT

From a consideration of the study of multiple exostosis it may be concluded that in the stabilized stage of this disease calcium exchange differs little from that of a normal individual whether the abnormal subject is maintained on a calcium poor or a calcium rich diet.

In the progressive stage of the disease calcium metabolism is markedly different from the normal in that calcium is lost from the body in relatively large amounts when the subject is maintained on a calcium poor diet. This excessive elimination of calcium is excreted by both the urine and feces in a normal ratio. When placed on a calcium rich diet, calcium is retained in the body to an extent not widely different from that in normal subjects. A resumption of a calcium poor diet again induces excessive calcium elimination.

In the stabilized stage of multiple exostoses, magnesium excretion is from two to three times as great as the intake, whether the subject is maintained on a diet poor or rich in magnesium. In the progressive stage of the disease, the general type of magnesium excretion resembles that of the stabilized stage but the degree of elimination is not so marked. Magnesium added to the diet in the stabilized stage results in the prompt excretion of the magnesium. The same test applied to the progressive stage gives evidence of the retention of some magnesium. The degree of retention, however, is much less than that shown by normal individuals.

Absorption of both calcium and magnesium in multiple exostosis is not inferior to that of normal subjects

The facts enumerated suggest that in the early stages of this proliferative type of bone disease under discussion a check may perhaps be given to the progress of the disease by proper dietary procedure (A complete report of the calcium and magnesium metabolism will be published in the *Journal of Experimental Medicine* )

#### PATHOLOGY

It seems to be the general opinion that the process of increased bone formation in these cases is derived from collections of cartilage cells during the transitional period from cartilage to bone, but this is of secondary importance. There is evidence of vicious cartilage growth, with very slow ossification, as is shown by the character, enlargement, fusion, malformation and bowing of the ends of the long bones. If, however, the growths are developed only from the cartilaginous forming bone, it is difficult to account for the origin of the growths on the other bones, such as on the skull and face. It is true, that these growths are more rare, but that does not change the theory as to the origin. Growths on the shaft of the bone are not different from those occurring near the ends and their origin may be the same. Some of these growths appear to have their origin from the periosteum, for as far as can be determined, the cortex of the shaft is intact, these must have occurred a considerable time after the formation of the bone. Other growths which cannot be differentiated from the bone itself must have had their origin during or before the formation of the bone.

The growths are variously described, owing to the fact that the examinations were made at different ages and developmental periods. A growth may be developed so completely that it cannot be differentiated from the normal bone having periosteum, cortex and medullary canal. In the stages where ossification has not yet taken place, these growths, some with large collections of nonregulated cartilage cells embedded in a spongy, more or less fibrous matrix, may have a membrane or periosteum surrounding them. Later the central spongy tissue may become more compact and bone cells may be found in or near the periphery. Frequently the periphery of the growth is solid, compact cartilage and areas of calcium and internally cellular tissue are sometimes seen. Calcification in irregular areas occurs while the cartilaginous growth is still active. Differentiation apparently only occurs when active cartilaginous growth has ceased.

An examination of the growth removed from the femur in case G demonstrated the following

There is a thick layer of dense connective tissue which represents the periosteum (Figs 32 and 33). It contains numerous dilated and congested blood vessels. On its internal surface groups of large, elongated cells can be seen. They have large vesicular nuclei and show a regular placed arrangement in one row, resembling epithelial cells. These osteoblasts cover the surface of the thick layer of compact bone and cartilaginous tissue, which forms the periphery of the nodule. From the periphery similar trabeculae of bony tissue can be followed also into the interior. Near the surface smaller or larger cavities with walls of compact bone can be seen, deep in the interior,



Fig 32—Periosteum and bone including precartilaginous  $\times 150$

however, only bony spiculae are found surrounded sometimes with dilated and engorged blood vessels. The interior mainly is made up of loose connective tissue (mostly fat) which is richly supplied by a network of blood vessels.

These are dilated and form rich anastomosis. Hemorrhages which may be the result of traumatism are quite numerous, and free blood may fill sinuses in the loose connective tissue. Sometimes only narrow strands of connective tissue, covered with a row of osteoblasts, separate the blood vessels from the spiculae. The bone tissue in the periphery as well as in the interior (trabeculae, spiculae) is compact in structure.



and shows no regular arrangement in Haversian system. The Howship cavities of absorption are also missing. The surfaces are smooth, and there is no medullary canal with bone marrow. Here and there, however, a few lymphocytes are seen. Scattered on the surface there are numerous imperfectly developed cartilaginous nodules, which form imperceptible transitions to the bony tissue. These nodules vary in size and often only a small cartilaginous area can be seen included in the bony tissue. The cartilage cells are irregular in shape and size. They are in large part closely packed, giving the typical picture of pre-cartilaginous tissue. This is surrounded with perichondrium, which is



Fig 33—Bone with the osteoplastic connective tissue  $\times 150$

sometimes continuous with the periosteum (A complete pathologic study is being made and will be reported in the near future by Dr N M Alter )

In a great deal of the literature apparently no difference has been made between the multiple cartilaginous exostosis and mechanical or traumatic exostosis. In the older reports of cases this has made it exceedingly difficult to tabulate and analyze the results. A good deal of the conflict of opinion regarding exostosis is because of this failure to differentiate the two conditions. The frequency of the occurrence of malignancy in these growths cannot be determined for this very reason.

## ANALYSIS OF REPORTED CASES

In a detailed analysis and classification of sixty-six reported cases, information was obtained which supports certain suggestions and opinions of the present paper

*Age Incidence*—Of sixty-six cases, fourteen occurred between 1 and 10 years of age, seven between 10 and 15 years, eleven between 15 and 20 years, nine between 20 and 25 years, ten between 25 and 30 years, and fourteen over 30 years of age

*Sex*—Of sixty-three cases, there were forty-seven males and sixteen females

*Hereditary History*—In thirty-three cases, a positive history of heredity was obtained in thirteen, the disease having occurred in some member or members of the patients' families. In one case, eight members were affected, and in several other cases many members were similarly affected

*Beginning of Growth*—In one case the growths were noticed at birth, in twelve cases they were noticed between birth and 5 years of age. Between the age of 5 and 10 years, there were seven cases, between 10 and 15 years, four cases, between 15 and 20 years, two cases, and in one case growths were noticed after 20 years of age. The remaining cases gave no definite information

*Cessation of Growth*—Only twelve patients gave information in this respect. In six cases growth ceased after operation, and in one it progressed, in one case it ceased at puberty, in one case after 11 months of age, and in three cases at 17, 22 and 25 years, respectively

*Order of Frequency*—The femur was affected in 43 cases, tibia in 35 cases, humerus in 29 cases, fibula in 27 cases, radius in 25 cases, ulna in 24 cases, phalanges in 20 cases, ribs in 19 cases, scapula in 17 cases, pelvic bones in 13 cases, clavicle and metacarpals in 12 cases each, metatarsal bones in 6 cases, skull bones in 6 cases, knee in 4 cases, the spine and tarsal bones in 2 cases each and the sternum in one case

*Position of Growth*—Femur. Diaphysis was affected most frequently, condyles next, and then the epiphysis and trochanters. Tibia. The upper extremity showed more frequent changes, then the lower end of the shaft, epiphysis and near epiphysis. Fibula. This bone showed changes in approximately the same order of frequency as the tibia. Humerus. In the majority of cases the shaft was affected, and in only one case was the epiphysis attacked. Growths near the epiphysis were the second most common occurrence. Radius and ulna. The carpal extremity in both these bones showed changes most often, and the diaphysis and epiphysis with equal frequency. Phalanges. There was no predominating change in any of the phalanges either in posi-

tion or in any particular phalanx The hands were more affected than the feet Ribs The middle of the ribs were affected mostly, particularly the third, fifth, sixth, eighth and tenth ribs Scapula The vertebral border and the spine were more frequently mentioned than other parts of the bone Pelvis The ilium and especially the crest were the parts most frequently affected Clavicle The acromial end and the near acromial end were more often affected than the sternal end or the middle Metacarpals Both epiphysis and diaphysis were attacked, otherwise no significant change predominated in any one part Metatarsals Both epiphysis and diaphysis Skull bones The face bones were affected in three cases and the frontal, temporal and occipital areas in one case each

### RÉSUMÉ

Multiple cartilaginous exostosis is a disease with the following distinctions

- 1 It presents hereditary factors
- 2 It is a disease with definite, well defined metabolic disturbances
- 3 There is no evidence that infection plays a part
- 4 It begins in early life, and probably before birth
- 5 It occurs more in males than females
- 6 It gives rise to obvious bone changes, inhibitory and stimulatory and at an age not yet determined
- 7 The long bones and flat bones are affected
- 8 Both epiphysis and diaphysis are involved
- 9 Malformation and deformities occur at an age not yet determined, due to arrest in growth of the skeleton and to bone growths arising at such points as to interfere with the normal growth and direction of the bones

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# TOXIC JAUNDICE IN PATIENTS UNDER ANTI-SYPHILITIC TREATMENT

A STUDY OF THE CHEMICAL ANALYSES OF THE BLOOD AND URINE, AND  
OBSERVATIONS ON THE EFFECT OF EXERCISE AND DIET  
IN THE TREATMENT OF SYPHILIS \*

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The treatment of syphilis by injections of arsenobenzol derivatives is, at times, accompanied by more or less grave signs of intoxication. Of these, three distinct types seem to arise. In the first type, symptoms of general malaise shortly follow the administration of the drug and, as a rule, pass off within twenty-four hours. In the second and third types, toxic symptoms may be delayed and not appear until several months after the cessation of treatment. The most pronounced symptoms are associated with the skin or liver.<sup>1</sup> The skin lesion usually develops in the course of the treatment as a maculopapular eruption with considerable thickening. This rapidly becomes generalized. Desquamation is profuse, leaving a thickened, cyanosed and frequently pigmented surface. Pustulation is common. The patient becomes debilitated and has a slight fever. The liver and spleen are frequently enlarged. The urine shows a trace of protein and bile pigment. Patients whose liver symptoms predominate may pass several weeks in apparently good health following their course of treatment, and then come under observation with general malaise and jaundice. The latter, at first slight, becomes more pronounced. The liver, and frequently the spleen, becomes enlarged and tender. The blood pressure, pulse and temperature are usually low. Symptoms as in acute yellow atrophy of the liver may supervene,<sup>2</sup> or the patient may slowly convalesce.

A jaundice of the above type, occurring during the secondary stage of syphilis, has frequently been described. Rolleston,<sup>3</sup> reviewing the literature on this subject, points out that this condition has frequently arisen in untreated cases and is not necessarily due to medication. Such cases improve under antisyphilitic treatment. The cases

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1 Harrison, L. W. *Quart J Med* **10** 291 (July) 1917.

2 Willcox, W. H. *Lancet* **1** 869 (May 24) 1919.

3 Rolleston, Sir Humphry. *Diseases of the Liver, Gallbladder and Bile Ducts*, London, 1912.

recognized as arsphenamin poisoning, on the other hand, are greatly aggravated by treatment. Untreated cases, in which jaundice and its associated signs occur coincidentally with the syphilitic skin lesions, bear a marked resemblance to many of the arsphenamin cases in which a mild jaundice is associated with severe dermatitis. It is possible that the arsenic in these cases simply accentuates a reaction which, to a mild degree, is ordinarily present in syphilis.

#### PREVENTIVE MEASURES

Unfortunately, the susceptible patients cannot be recognized, and, in spite of all precautions, the first intimation of trouble is the onset of the severe toxic symptoms. Of precautionary measures in administering treatment, the examination of the urine for signs of nephritis is recommended.<sup>4</sup> Few of the cases, however, show such signs, and, on the whole, the kidneys are impaired but slightly, if at all. Testing the urine for bile pigment is equally of little use as the warning does not come in time. Of greater value in determining the state of jaundice is the test for bile pigment in the blood serum or plasma, and for this Gmelin's test is quite satisfactory.<sup>5</sup> It is generally conceded that the development of any untoward symptom in the course of treatment should be considered carefully before further injections are given. The size and frequency of the dose have both been reduced greatly; Willcox and Webster<sup>6</sup> recommend 0.3 gm. of arsphenamin or similar preparations (which is half the original dose) and the interval between doses to be two or three weeks. In using full doses (0.6 gm.), they recommend an interval of four weeks between injections. These intervals permit a complete elimination of the arsenic before a succeeding dose is given. Harrison,<sup>1</sup> referring to the cumulative effect of these remedies, states that "patients who have shown the most toxic effects have, in the majority of instances, done so after a number of doses have been administered." In a number of his cases, in which the intervals between treatments was sufficiently long to permit the excretion of all the arsenic, toxic symptoms developed after several treatments. He suggests that each succeeding dose contributes its quota to the damage, and finally definite toxic symptoms are precipitated by a final dose.

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<sup>4</sup> See Reference 23.

<sup>5</sup> Considering that bilirubin is frequently found in the plasma of apparently healthy individuals, its determination by chemical methods is of little diagnostic value. Its repeated quantitative estimation in a particular case is an aid in following the course of the illness. The quantitative method described by Blankenhorn is of value in this respect. Blankenhorn, M. A. *Tr. A. Am. Phys.* 1917.

<sup>6</sup> Willcox, W. H., and Webster, J. *Brit. M. J.* 1:473 (April 1) 1916.



Conditions similar to acute yellow atrophy of the liver have frequently been observed following combined mercurial and arsenical treatment,<sup>7</sup> and it is of interest to recall that such symptoms have followed mercury alone.<sup>8</sup> In selecting the dose of arsenic in these cases, the added toxic factor of the mercury must be considered. As a preventive of immediate toxic symptoms, Westrope<sup>9</sup> reports favorable results from the use of a milk diet for twenty-four hours before the injection of the drug.

#### EXAMINATION OF CASES

An opportunity was afforded of making a chemical examination of the blood and urine in twenty-five cases of toxic jaundice following antisyphilitic treatment, and in fifteen cases convalescent or recovered from other illnesses. At the time of the examinations, the patients had shown toxic symptoms for periods ranging from 16 to 136 days, the majority were still slightly debilitated, others had apparently recovered. Six had bile pigment in the urine. None of the patients had proteinuria or other sign of nephritis, although in some cases the clinical history indicated that such symptoms had been present in the course of the illness. The antisyphilitic treatment in these cases consisted of an intravenous injection of novarsenobenzol (Billon) and a synchronous intramuscular injection of mercury, the doses being repeated at intervals of seven days.

#### CASE HISTORIES

CASE 1—Male, aged 55, weight 116 pounds, no history of previous illness or infection.

October, 1918 Weakness, precordial pain and palpitation.

June 27, 1919 General weakness, liver 5 inches below costal margin, spleen, enlarged, blood pressure, 122/72, temperature, normal, hemoglobin, 53 per cent, red cells, 3,736,000, Wassermann, +++.

*Diagnosis*—Syphilitic hepatitis.

CASE 2—Male, aged 23, weight 158 pounds. March 7, 1919 Exposure, sore discovered on penis the following day. Received novarsenobillon, 1.05 gm and mercury, 0.128 gm, in two treatments with an interval of seven days. Following the second treatment he developed "swelling of the face" and nausea. He later became jaundiced.

April 4 Urine contained a trace of protein and bile pigment.

May 11 Well-marked icterus, liver at costal margin, spleen, not palpable, blood pressure, 130/80.

June 13 No arsenic found in urine seventy-four days after last treatment.

June 20 Urine constantly contained bile pigment, at times a trace of protein and on one examination tyrosin. He has never given a positive Wassermann reaction.

June 27 Chemical blood analysis. Clinical findings negative.

<sup>7</sup> Severin. *Ztschr klin Med* **76** 138, 1912, Bedig. *Munch med Wchnschr* **62** 1140, 1915.

<sup>8</sup> Tileston, W. *Boston M & S J* **158** 510, 1908.

<sup>9</sup> Westrope. *Brit M J* **2** 456, 1916.

CASE 3—Male, aged 24, weight, 155 pounds Jan 25, 1919 Chancre

March 6 Combined treatment instituted, received novarsenobillon, 4.05 gm, and mercury, 0.45 gm, in seven treatments with seven day intervals Following the fifth treatment, nausea and jaundice developed

May 11 Slight icterus, liver 1 inch below costal margin, urine showed a trace of protein, no bile pigment, leucin, tyrosin or bile salts

June 17 No arsenic found in urine fifty-two days after last treatment

June 27 Chemical blood analysis Clinical findings, aside from slight debility, were negative

CASE 4—Male, aged 34, weight, 146 pounds Dec 26, 1918 Chancre

March 30, 1919 Had received novarsenobillon, 4.05 gm, and mercury, 0.45 gm, in seven treatments with seven day intervals He became ill and jaundiced after the last injections

May 11 Marked jaundice, liver, 1.5 inch below costal margin, spleen, slightly enlarged, blood pressure, 128/86 Bile pigment in urine, no protein, leucin or tyrosin

June 13 No arsenic found in urine seventy-one days after last injection

June 27 Chemical blood analysis Clinical findings, aside from slight debility, were negative

CASE 5—Male, aged 24, weight, 134 pounds Jan 1, 1919 Chancre

March 8, 1919 Had received novarsenobillon, 4.65 gm, and mercury, 0.518 gm, in eight treatments with intervals of seven days

May 14 Jaundice developed

May 20 Slightly jaundiced, pupils unequal, liver tender and 1½ inch below costal margin, spleen not palpable, blood pressure, 128/80 Urine contains a trace of bile pigment, no protein

June 13 No arsenic found in urine ninety-three days after last injection

June 27 Chemical blood analysis Clinical findings, aside from slight debility, were negative

CASE 6—Male, aged 24, weight, 150 pounds July, 1917 Received novarsenobillon, 4.05 gm, and mercury, 0.45 gm, in seven treatments with intervals of seven days Following this he was somewhat debilitated These treatments were repeated in October, 1918, and again in January, 1919 In May, 1919, he had an abscess of the left buttock associated with severe generalized furunculosis and great weakness Liver was tender and 1½ inch below costal margin Spleen, palpable Wassermann, negative Urine, contained a trace of bile pigment, no protein Blood pressure, 110/67

June 17 No arsenic found in urine 117 days after last injection

July 1 Chemical blood analysis Abscesses healed Debilitated

CASE 7—Male, aged 20, weight 155 pounds March 20 1919 Chancre

May 8, 1919 Had received novarsenobillon, 4.05 gm, and mercury, 0.388 gm, in six treatments with intervals of seven days Following the fourth injection he became febrile, and following the sixth injection he developed anorexia, jaundice and constipation, later, diarrhea

May 24 Diarrhea, sclera jaundiced, skin clear, liver, palpable and tender, blood pressure, 100/65 Wassermann, negative

June 13 Repeated urinalysis showed nothing abnormal No arsenic found in urine thirty-six days after last injection

July 1 Greatly improved Chemical blood analysis

CASE 8—Male, aged 42, weight, 163 pounds Dec 5, 1918 Chancre

Feb 4, 1919 Had received novarsenobillon, 4.05 gm, and mercury, 0.45 gm, in seven treatments with intervals of seven days Eleven days after the last injection, he developed pains in the chest and abdomen, weakness and constipation Liver, 1½ inch below costal margin, spleen, palpable, Wassermann, negative, urinalysis, normal

May 7 Apparently recovered Given seven days' leave

May 14 Returned markedly jaundiced, complaining of anorexia, weakness and a "distended feeling" in the liver region Liver,  $1\frac{1}{2}$  inch below costal margin, tender Urine contained a large amount of bile pigment, no protein Wassermann, negative

June 13 Urine free from bile pigment, protein, leucin, tyrosin and bile salts No arsenic found in the urine 129 days after last injection

July 1 Chemical blood analysis Skin still discolored and he suffered from slight debility

CASF 9—Male, aged 33, weight, 147 pounds January, 1919 Chancre

April 8, 1919 Had received novarsenobillon, 1.65 gm, and mercury, 0.194 gm, in three treatments with intervals of seven days He became jaundiced after the last injection Wassermann, negative

May 22 Thin, distinctly jaundiced, liver, 1 inch below costal margin Blood pressure, 108/70 Urine contained bile pigment, no protein

June 13 No arsenic found in the urine sixty-seven days after the last injection Aug 1 Chemical blood analysis Slightly debilitated

CASE 10—Male, aged 31, weight, 137 pounds Jan 23, 1919 Chancre

April 10, 1919 Had received novarsenobillon, 5.1 gm, and mercury, 0.58 gm, in nine treatments with intervals of seven days April 23 Slight jaundice, gingivitis, ulceration of left cheek, weakness Liver, tender, 2 inches below costal margin Spleen, enlarged Urinalysis, negative No arsenic found in urine fifty-six days after last injection

August 1 Chemical blood analysis Jaundice had disappeared, liver and spleen were greatly reduced in size, and he had no complaints

CASF 11—Male, aged 34, weight, 136 pounds November, 1918 Chancre

December-January, 1919 Received novarsenobillon, 4.05 gm, and mercury, 0.5 gm, in seven treatments with intervals of seven days

April 15, 1919 Anorexia, nausea and jaundice

May 1 Slight debility, moderately jaundiced, blood pressure, 112/78 No arsenic found in the urine 157 days after the last injection

July 7 Chemical blood analysis Liver had not decreased in size, otherwise his clinical findings were negative

CASF 12—Male, aged 32, weight, 146 pounds Ulcer on penis in 1911, for which he took pills for a period of eight weeks Gassed in September, 1918 February, 1919 Urethritis, four weeks' treatment

March 7, 1919 Received one injection of novarsenobillon, 0.45 gm, furuncles appeared on legs and treatment was stopped

April 26 Severe generalized dermatitis Liver  $2\frac{1}{2}$  inches below costal margin Spleen enlarged Urine contained bile pigment Wassermann, negative No arsenic found in urine 125 days after last injection

August 7 Chemical blood analysis The liver and spleen had not decreased in size, the former, however, had lost its tenderness The skin lesions had cleared up and he had no complaints

CASE 13—Male, aged 29, weight, 144 pounds December, 1915 Chancre February, 1916 Received three injections of arsphenamin

June, 1916 Developed a second sore on penis Received arsphenamin, 5.95 gm, and mercury, 0.64 gm, in ten treatments ending in September, 1917 Late in September, he developed nausea, vomiting, and general debility, necessitating six weeks hospital treatment

January, 1919 Wassermann strongly positive He received novarsenobillon, 2.25 gm, and mercury, 0.26 gm, in four treatments with intervals of seven days

May 2 Headache, coated tongue, constipation and jaundice Liver  $1\frac{1}{2}$  inch below costal margin Spleen, not palpable Blood pressure, 115/80 Urine contained a trace of protein and bile pigment

June 13 Urine free from protein, bile pigment, leucin, tyrosin and bile salts No arsenic was found in the urine ninety days after the last injection

July 7 Chemical blood analysis General condition had improved Urine free from protein and bile pigment for two months Liver and spleen still enlarged

CASE 14—Male, aged 23, weight, 138 pounds October, 1918 Chancre Received novarsenobillon, 465 gm, and mercury, 0.5 gm, in eight treatments with intervals of seven days, terminating Dec 28, 1918

April 28, 1919 Anorexia, followed in one week by pain in the liver region and jaundice

May 10 Anorexia, constipation and jaundice Liver, tender, 1½ inch below costal margin Spleen, slightly enlarged Blood pressure, 115/62 Urine contained bile pigment

June 7 Jaundice disappeared No arsenic found in the urine 180 days after last injection

July 7 Chemical blood analysis General condition had greatly improved, liver and spleen slightly decreased in size

CASE 15—Male, aged 22, weight, 135 pounds February, 1916 Nephritis, all eight months, recurrences in July, 1917, and May, 1918 February, 1919 Chancre

March 4, 1919 Combined treatment instituted Received novarsenobillon, 295 gm, and mercury, 0.324 gm, in five treatments with intervals of seven days Nephritic symptoms developed

May 14 Liver and spleen not palpable Blood pressure, 125/80 No complaints Urine contains a trace of bile pigment, protein and an occasional hyalin and granular cast

August 7 Chemical blood analysis Free from symptoms Wassermann, negative

CASE 16—Male, aged 20, weight, 137 pounds December, 1918 Chancre Feb 14, 1919 Had received novarsenobillon, 4.05 gm, and mercury, 0.45 gm, in seven treatments with intervals of seven days

May 10 Severe abdominal pains, followed by slight jaundice

May 15 Slightly jaundiced, liver, palpable, not tender, spleen, not palpable Blood pressure, 128/80 Urine contains a trace of protein and bile pigment, no bile salts or casts Wassermann, negative No arsenic found in urine eighty-eight days after last injection

August 7 Chemical blood analysis Jaundice had disappeared, liver was at costal margin, and he had no complaints

CASE 17—Male, aged 24 Jan 1, 1919 Chancre

April 4 Had received novarsenobillon, 4.05 gm, and mercury, 0.45 gm, in seven treatments with intervals of seven days Following the third treatment, general malaise Following the sixth treatment, severe dermatitis, which became greatly aggravated following the seventh and last treatment

April 10 Marked gingivitis, stomatitis and purulent conjunctivitis Skin brawny red with copper colored papules Marked exfoliation Blood pressure, 115/80 Liver not palpable Urine contains bile pigment, protein, cholesterol, a few red blood cells and granular casts

April 25 Liver 2 inches below costal margin Spleen, enlarged Dermatitis improving

June 6 Urine contains bile salts, no bile pigment August 13 Chemical blood analysis General condition had greatly improved The skin remained thickened and there was a slight desquamation Liver and spleen had decreased in size Wassermann, negative

CASE 18—Male, aged 23 Feb 7, 1919 Chancre

March 14 1919 Had received novarsenobillon, 2.85 gm, and mercury, 0.32 gm in five treatments with intervals of seven days March 20 Developed a severe dermatitis April 10 Skin thickened, purplish red, with a fine papular

eruption and marked scaly exfoliation Moderate stomatitis and conjunctivitis Liver and spleen not palpable Blood pressure, 100/60 Urine contains bile pigment and salts, no leucin or tyrosin

April 25 Liver 1 inch below costal margin White blood cells, 17,200 Temperature, from 99 to 100 F

May 9 Spleen, palpable

July 13 Chemical blood analysis Recovered from dermatitis Liver and spleen still palpable Wassermann, negative Urine contained no arsenic ninety-one days after last injection

CASE 19—Male, aged 36 Received novarsenobillon, 4.05 gm, and mercury, 0.45 gm, in seven treatments with intervals of seven days, the course terminating in April, 1919 No immediate reaction Wassermann, negative

May 29, 1919 Returned from seven days' leave complaining of drowsiness, anorexia, nausea, clay colored stools and jaundice

July 2 Markedly jaundiced, liver, palpable, tenderness over gallbladder Urine contained bile pigment, a trace of protein and an occasional granular cast No arsenic found in urine seventy-five days after last injection

July 13 Chemical blood analysis Clinical findings remained unchanged, excepting for the absence of protein and casts in the urine

CASE 20—Male, aged 21 Typhoid, 1910 Gonorrheal urethritis and prostaticitis, February to May, 1919

June 24, 1919 Weakness, nausea and jaundice Liver and spleen palpable

July 13 Chemical blood analysis Jaundice and subjective symptoms had disappeared Liver and spleen still palpable

CASE 21—Male, aged 27 Psoriasis April 20, 1919 Chancre

June 11, 1919 Had received novarsenobillon, 3.45 gm, mercury, 0.32 gm, in seven treatments with intervals of seven days Following the third injection, chills, headache and muscular stiffness, following the fourth injection, a maculopapular eruption

June 25 Marked generalized dermatitis with profuse desquamation Liver, 1½ inch below costal margin Wassermann, negative No arsenic found in urine thirty-two days after last injection

July 13 Chemical blood analysis Clinical findings unchanged

CASE 22—Male, aged 37 Dec 15, 1918 Chancre

Jan 29, 1919 Had received novarsenobillon, 3.45 gm, and mercury, 0.388 gm, in six treatments with intervals of seven days Following the fifth treatment an eruption appeared on the neck

March 31 Wassermann, negative A trace of protein in the urine

April 12 Moderate conjunctivitis, skin red, with diffuse dark papules, slight desquamation Liver, palpable Blood pressure, 96/60 Urine contains a trace of bile pigment and protein

April 25 Marked generalized desquamation Liver, 2 inches below costal margin Spleen, enlarged Several abscesses on thighs and neck No trace of arsenic in 50 gm of skin flakes

May 16 Abscesses healed Desquamation slight Skin markedly pigmented Blood pressure, 125/80 Liver and spleen as before Temperature, from 99 to 103 F for past three weeks Complains of numbness in feet White blood cells, 14,000

June 9 Urine free from bile pigment, bile salts, protein, leucin, tyrosin and casts Wassermann, negative No arsenic found in urine 135 days after last injection

July 17 Chemical blood analysis General condition greatly improved

CASE 23—Male, aged 23 Feb 27, 1919 Chancre

May 5, 1919 Had received novarsenobillon, 2.85 gm, and mercury, 0.32 gm, in five treatments with intervals of seven days This was immediately followed by a severe generalized dermatitis, associated with marked desquamation and numerous small abscesses Urine contained a trace of protein

April 25 Deep pigmentation of skin, fine branny desquamation Liver and spleen enlarged Blood pressure, 115/70 Loss of finger nails Urinalysis normal No arsenic found in urine seventy-four days after last injection  
July 17 Chemical blood analysis General condition improving, still a bed patient

CASE 24—Male, aged 22 June 13, 1919 Deeply jaundiced Urine contains bile pigment, protein and granular casts No history of syphilis or of treatment

July 2, 1919 Deeply jaundiced, liver and spleen palpable, indefinite pains in liver region, stools clay colored, appetite, good, Wassermann, negative

August 17 Chemical blood analysis Condition unchanged, excepting for the absence of protein and casts in the urine

CASE 25—Male, aged 21, weight, 160 pounds Feb 12, 1919 Had received novarsenobillon, 545 gm, and mercury, 0648 gm, in ten treatments with intervals of seven days

August 1 Anorexia, nausea and jaundice Liver and spleen not enlarged Urine contains bile pigment and bile salts No arsenic found in urine 125 days after last injection

August 17 Chemical blood analysis General condition fair, slightly jaundiced, liver not enlarged

CASE 26—Male, aged 21 April 21, 1919 Chancre

June 12, 1919 Had received novarsenobillon, 64 gm, and mercury, 071 gm, in eleven treatments with intervals of seven days

June 29 Chills, weakness, abdominal cramps, constipation and jaundice Wassermann, negative

July 7 Complaints of weakness, jaundice persists, liver, palpable No arsenic found in urine thirty-five days after last injection

July 17 Chemical blood analysis Condition unchanged

CASE 27—Male, aged 25 Feb 9, 1919 Chancre

March 17, 1919 Had received novarsenobillon, 405 gm, and mercury, 045 gm, in seven treatments with intervals of seven days

June 13 Weakness, constipation and jaundice

July 8 Deeply jaundiced Liver, slightly enlarged No arsenic found in urine ninety days after last injection

July 17 Chemical blood analysis General condition slightly improved

CASE 28—Male, aged 34 No history of infection April 10, 1919 Developed a generalized maculopapular eruption Wassermann, strongly positive

June 23, 1919 Had received novarsenobillon, 405 gm, and mercury, 045 gm, in seven treatments with intervals of seven days

June 27 Nausea, vomiting and jaundice

July 8 Jaundiced, liver, palpable, urine contains bile pigment, no complaints No arsenic found in urine twenty-four days after last injection

July 17 Chemical blood analysis General condition unchanged

CASES 29 to 34—These patients were recovering from illnesses other than toxic jaundice, and at the time of the chemical blood analyses were still in a weakened condition

CASES 35 to 40—These men were apparently in good health at the time of the chemical blood analyses

#### METHODS EMPLOYED

A complete twenty-four hour specimen of urine was collected from each patient on the day preceding the blood analysis On these specimens were determined the volume, reaction, specific gravity, protein, sugar, bilirubin, bile salts, urobilinogen, urobilin, uric acid and the microscopic contents

Synchronous blood and urine specimens were collected on the following morning before breakfast, by the following method At 6 a m the patient completely emptied his bladder, at 7 30 a m, from 30 to 40 c c of blood was aspirated, by venipuncture, into a bottle containing potassium oxalate crystals (20 drops of 20 per cent potassium oxalate solution evaporated on the bottom and sides of the bottle), at 9 a m, the three-hour specimen of urine was collected In some cases, when the urinary excretion was low, a glass of water was given during this period

The following estimations were made on the whole blood Sugar, creatinin, cholesterol, urea nitrogen, uric acid and bile salts Bilirubin tests were made on the plasma

On the three hour specimens of urine, the following determinations were made Rate of excretion, reaction, specific gravity, the presence of bile salts and protein, and, quantitatively, sugar, uric acid, urobilinogen, urobilin and bilirubin

Sugar in the urine was estimated quantitatively by Myers' method,<sup>10</sup> bilirubin, by Hooper and Whipple's modification of Huppert's reaction,<sup>11</sup> bile salts were estimated by Hay's sulphur test Urobilinogen was tested by extracting with amyl alcohol after developing the color in the urine by the use of Ehrlich's reagent, diluting to a suitable volume with amyl alcohol, and obtaining relative quantitative figures by matching against a standard solution in a Hellige colorimeter The relative rate of excretion was obtained by multiplying this figure by the c c per hour of urine and dividing by 1,000

Urobilin estimations in the urine were made by extracting with amyl alcohol and adding to this an ammoniacal alcoholic solution of zinc chlorid, relative quantitative figures were obtained by repeated alcoholic dilutions until no fluorescence could be detected on examining in sunlight against a black background The relative rate of excretion was obtained by multiplying the dilution by the c c per hour of urine and dividing by 100 The relative oxidation of urobilinogen was obtained by dividing urobilin by urobilinogen Uric acid in the urine was quantitatively determined by the method of Benedict and Hitchcock<sup>12</sup> Blood sugar estimations were made by a modification of the Lewis and Benedict method<sup>13</sup>

Creatinin in the blood was estimated by Folin's method as modified and described by Myers and Killian<sup>14</sup> Blood cholesterol was deter-

10 Myers, V C Proc Soc Exper Biol & Med **13** 178, 1916

11 Hooper, C W, and Whipple, G H Am J Physiol **40** 332, 1916

12 Benedict, S R, and Hitchcock, E H J Biol Chem **20** 619, 1915

13 Myers, V C, and Bailey, C V J Biol Chem **24** 147, 1915

14 Myers V C, and Killian, J A Am J M Sc **157** 674, 1919

nined by the method described by Myers and Wardell,<sup>15</sup> urea nitrogen in the blood, by Van Slyke and Cullen's modification of Marshall's method,<sup>16</sup> uric acid in the blood, by the Folin and Denis-Benedict method as described by Myers and Fine<sup>17</sup>

The presence of bile salts in the blood was determined by applying Pettenkofer's test to the supernatant fluid, after the precipitation of the purins, in the method for estimating the blood uric acid, 10 c c of blood was used in this test Gmelin's test for bilirubin was applied directly to the plasma Bilirubin in the plasma was also estimated by the method described by Blankenhorn<sup>5</sup> and found to correspond with the results of Gmelin's test The method consists in diluting the plasma until a color can barely be detected in a column 1 cm deep, the number of dilutions is the bilirubin index

A modified Gutzeit's test<sup>18</sup> was used for arsenic, 50 c c of urine being employed

#### DISCUSSION

*Excretion of Arsenic*—No arsenic was found in the urine of any of these patients, tests were made at periods varying from 24 to 157 days after the last treatment

*Analyses of Twenty-Four-Hour Urines*—The twenty-four-hour urines of all these patients were free from protein and pathologic sediment No bile salt was indicated by Hay's test Six of the patients clinically jaundiced had bile pigment in the urine, the method used was found unsuitable for accurate quantitative determination of small quantities

The relative rate of excretion of urobilinogen and the relative oxidation of this substance to urobilin are shown in Table 1, and will be referred to later The daily excretion of sugar is shown in Table 1 to be normal in all of the cases<sup>19</sup>—the amount not being detectable by ordinary methods The daily excretion of uric acid was much greater in the more severe cases

*Bilirubin, Urobilinogen, Urobilin*—In eleven cases, bile pigment was found in the plasma and, as a rule, in these cases bile salts were also found, although a few cases showed dissociation The extent of the jaundice did not correspond with the severity of the illness

In Table 3 the cases are grouped according to the presence or absence of bilirubin in the plasma, cases not associated with disordered liver are classified by the presence or absence of debility The greatest

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15 Myers, V C, and Wardell, E L J Biol Chem **36** 147, 1918

16 Van Slyke, D D, and Cullen, G E J Biol Chem **19** 211, 1914

17 Myers, V C, and Fine, M S J Biol Chem **20** 391, 1915

18 Simon W Manual of Chemistry, New York, 1916

19 Bailey, C V Arch Int Med **23** 455 (Oct) 1919



excretion of urobilinogen and urobilin was noted in the jaundiced cases, in the liver cases which were free from jaundice the output of this pigment was less than half. Among the cases not associated with liver disturbance, the debilitated patients had twice the excretion of the well patients. A relatively higher rate of excretion of urobilinogen and urobilin was present in the early morning than, on the average, during the day. This was most marked in the severe cases, the early morning rate being 19.66 per hour, while for the twenty-four-hour period the rate was 13.4 per hour. The difference in the liver cases in which improvement was noted was less marked, being 8.6 per hour in the morning and 7.6 per hour in the twenty-four-hour specimens.

TABLE 1—TWENTY-FOUR-HOUR URINE

Case	Volume, Cc	Bilirubin	Total Relative Excretion		Relative Oxidation of Urobilinogen	Uric Acid		Sugar, Gm in 24 Hrs
			Urobilinogen	Urobilin		Gm in 24 Hrs	Mg per Hr	
1	2,300	—	565.8	20.7	0.04	0.65	27.0	1.61
2	2,210	—	165.75	24.31	0.15	0.975	40.62	1.69
3	1,260	—	191.52	10.08	0.05	0.945	39.37	1.33
4	1,325	—	250.42	19.87	0.08	0.903	37.62	1.67
5	1,495	—	55.31	17.94	0.32	0.57	23.75	1.02
6	1,005	—	55.27	11.05	0.2	0.65	27.0	1.18
7	1,424	—	148.09	249.2	1.68	0.726	30.25	1.28
8	1,480	—	325.6	22.2	0.07	0.518	21.58	1.48
9	1,120	—	259.8	20.72	0.08	0.683	28.45	1.32
10	1,520	—	161.12	9.12	0.06	0.744	31.0	2.55
11	1,150	—	188.6	63.25	0.34	0.57	23.75	1.28
12	1,600	—	54.4	16.0	0.29	0.48	20.0	0.67
13	2,350	—	65.8	18.8	0.28	0.607	25.29	1.03
14	1,450	—	79.75	26.1	0.33	0.75	31.25	0.84
15	2,150	—	75.25	217.15	2.85	0.47	19.58	0.73
16	660	—	192.06	27.06	0.14	0.56	23.33	0.9
17	1,300	—	54.6	16.9	0.31	1.35	56.25	1.17
18	1,150	—	138.0	33.35	0.24			1.56
19	2,315	+++	451.42	131.95	0.29			1.39
20	1,470	—	51.45	42.63	0.83	0.715	29.79	0.88
21	740	+	63.64	66.16	1.04			1.18
22	1,470	—	52.92	164.64	3.11	1.4	58.33	1.23
23	2,030	—	36.54	64.96	1.77	0.574	23.91	1.14
24	1,700	++	88.4	149.6	1.69	0.83	34.58	1.22
25	1,150	++++	414.0	146.0	0.35	1.1	45.83	2.76
26	1,050	—	25.2	115.5	4.58	0.743	30.95	1.28
27	1,800	++	594.0	273.6	0.47	1.75	72.91	2.41
28	1,470	++++	117.6	211.68	1.8	1.62	67.5	2.47

*Oxidative Activity of the Urine*—In the voided urine, the relative oxidation of urobilinogen to urobilin was greatest in the well patients and least in the severe liver cases, indicating either the presence of a protecting substance or of a decreased excretion of oxidase in these cases. The latter is the probable explanation as in similar conditions—poisoning by phosphorus, chloroform, etc.—there is a decrease of oxidation in the body, as shown by the respiratory exchange and the presence of incompletely oxidized bodies in the urine<sup>20</sup>. In Table 3 the figures indicate not only a decreased excretion of oxidase in the liver cases, but also in debilitating conditions not clinically associated

20 Wells, H. G. *Chemical Pathology*, Philadelphia and London, 1918, p. 542

with disordered liver. Absolute rest seems to increase the excretion and probably the production of oxidase, in the twenty-eight liver cases the oxidative activity in the urine was greater in the early morning than in the twenty-four-hour specimens in the proportion of 59 to 49.

*Cholesterol*—Of greater interest is the concentration of cholesterol in the blood. In the twelve cases not associated with disordered liver, the percentage varied from 0.117 to 0.21, giving an average of 0.155 per cent, which compares favorably with Gorham and Myer's fourteen normal cases with an average of 0.15 per cent, using the same method.<sup>21</sup> Of the patients with catarrhal jaundice, one (Case 20) had recovered and showed a blood cholesterol of 0.153 per cent, a second patient (Case 24) was still deeply jaundiced and had a slight increase of this substance in his blood (0.184 per cent). The blood cholesterol in the case of syphilitic hepatitis is slightly above the average normal. In the twenty-five cases of toxic jaundice, the cholesterol value is strikingly high, giving an average of 0.235 per cent, the values varying from 0.165 per cent in a patient apparently recovered, to 0.292 per cent in a recent case. In 84 per cent of these cases, the value is over 0.2 per cent. In Table 3 one sees that the greatest concentration of cholesterol in the blood occurred in the cases in which bile pigment was found in the plasma. Hypercholesterolemia, however, was found in nearly all of the toxic cases and was present in the patients free from symptoms, while still under hospital treatment. It seems to be an early and marked sign of toxic jaundice and its presence may be a valuable sign of a precarious state of the liver in these cases.

*Sugar*—No disturbance of carbohydrate metabolism was discovered. The values for blood sugar are normal, in the last six cases the values are above normal, but these patients were examined three hours after breakfast and were influenced by alimentation. The excretion of sugar at the time of the blood analyses and for the twenty-four-hour period was at the normal rate.<sup>19</sup>

*Blood Urea and Creatinin*—A study of the nonprotein nitrogenous constituents of the blood is complicated by the high protein diets and the varying physical restrictions placed on these men. The values for urea nitrogen in the last six cases, the patients apparently being in good health, are within the upper normal limit, which is 20 mg per hundred c.c. of blood.<sup>22</sup> Of the remaining cases, some show normal values, but the majority are above normal, one as high as 49 mg per hundred c.c. That this increase is in part due to impaired elimination by the kidneys is shown by the fact that, with few exceptions, the cases with a urea nitrogen exceeding 20 mg per hundred show a slight

21 Gorham, F. D. and Myers, V. C. *Arch. Int. Med.* 20:599 (Nov.) 1917.

22 Kast, L., and Wardell, E. L. *Arch. Int. Med.* 22:581 (Nov.) 1918.

TABLE 2

Case	Day of Illness	Blood								Urine—			
		Bilirubin		Bile Salts	Cholesterol, per Cent	Sugar, per Cent	Gm per 100 C c			Sugar, Gm per Hr	Uric Acid, Mg per Hr	Index of Uric Acid Excretion*	Bilirubin
		Gmelin's Test	By Dilution of Plasma				Creatinin	Urea N	Uric Acid				
1	239	—		—	0.171	0.086	2.2	40	4.41	0.06	23.86	0.18	—
2	92	—		—	0.165	0.102	2.85	22	4.9	0.046	20.87	0.23	—
3	81	—		—	0.263	0.1	2.6	32	3.3	0.06	25.88	0.127	—
4	89	—		—	0.279	0.09	2.4	33	4.7	0.036	28.56	0.17	—
5	13	—		—	0.233	0.118	3.2	37	4.2	0.036	9.08	0.466	—
6	55	—	16	+	0.208	0.096	1.98	22	3.67	0.050	32.2	0.114	—
7	54	—	8	—	0.203	0.102	1.94	24	2.11	0.044	43.1	0.049	—
8	136	—	12	—	0.233	0.1	1.96	27	2.46	0.015	8.21	0.3	—
9	84	+	30	—	0.267	0.11	2.22	24	3.7	0.035	19.2	0.2	—
10	69	—	12	—	0.193	0.1	2.1	23	3.57	0.044	28.11	0.127	—
11	83	+	24	—	0.292	0.118	2.5	31	2.5	0.054	19.3	0.13	—
12	122	—	14	—	0.275	0.106	2.4	43	3.87	0.234	10.13	0.387	—
13	66	—	10	—	0.205	0.112	2.6	30	3.57	0.086	63.5	0.056	—
14	70	—	10	—	0.203	0.092	2.26	28	5.0	0.046	27.8	0.178	—
15	90	—	14	—	0.212	0.1	2.58	31	4.78	0.147	66.0	0.072	—
16	58	—	14	—	0.203	0.108	2.02	33	1.76	0.056	22.6	0.076	—
17	113	—	8	—	0.258	0.094	2.41	15	4.34	0.069	96.7	0.045	—
18	85	—	12	—	0.175	0.096	1.76	12	5.55	0.033			—
19	45	+++	150	+	0.222	0.108	1.74	8	1.94	0.048	56.7	0.034	+++
20	19	++	60	—	0.153	0.108	1.54	11	3.12	0.032	20.5	0.156	—
21	45	+	40	+	0.292	0.096	1.8	14	5.31	0.034	60.5	0.087	+
22	170	—	12	—	0.285	0.124	2.13	14	5.0	0.045	44.6	0.11	—
23	74	+	50	+	0.17	0.12	2.8	30	3.0	0.07	44.6	0.066	—
24	34	+++	120	+	0.184	0.084	1.5	20	3.7	0.054	50.0	0.074	++
25	16	++++	80	+	0.24		1.8	36	6.3	0.2	168.6	0.037	++++
26	18	+	50	+	0.292		1.7	16	2.39	0.148	95.0	0.025	—
27	34	++	80	++	0.275		1.3	29	3.1	0.052	66.0	0.047	++
28	20	++	90	+++	0.237	0.116	1.2	39	1.5	0.055	53.4	0.028	++++
29		—		—	0.21	0.1	2.3	36	5.54	0.03	31.0	0.178	—
30		—		—	0.12	0.102	2.0	34	6.4	0.027	26.2	0.246	—
31		—		—	0.16	0.112	2.1	36	2.3	0.105	103.1	0.022	—
32		—		—	0.18	0.108	1.9	47	3.3	0.052	27.3	0.037	—
33		—		—	0.15	0.1	1.98	41	5.45	0.104	89.4	0.2	—
34		—		—	0.117	0.088	1.84	49	3.23	0.098	64.0	0.05	—
35		—		+	0.19	0.124	2.3	16	2.32	0.014	8.0	0.29	—
36		—		—	0.12	0.112	2.1	18	3.0	0.03	34.0	0.035	—
37		—		—	0.17	0.12	2.0	19	3.3	0.035	47.2	0.07	—
38		—		—	0.137	0.12	2.1	20	2.4	0.028	35.6	0.066	—
39		—		—	0.15	0.118	2.1	18	5.6	0.033	54.8	0.1	—
40		—		—	0.16	0.128	2.1	20	1.7	0.024	35.7	0.046	—

\* Milligrams per 100 C c of blood divided by milligrams per hour excreted

TABLE 2

—Urine			Diet					Diagnosis	Remarks
Relative Excretion Rate per Hr		Relative Oxidation of Urobilinogen	Protein			Fat, Gm	Carbohydrate, Gm		
Urobilinogen	Urobilin		Animal, Gm	Vegetable, Gm	Total Gm				
52.64	2.24	0.04	90	60	150	152	435	Syphilitic hepatitis	Debilitated unrestricted up and about
3.18	0.73	0.23	90	60	150	152	435	Toxic jaundice	
1.37	0.66	0.48	90	60	150	152	435	Toxic jaundice	
3.68	0.80	0.22	90	60	150	152	435	Toxic jaundice	
1.85	1.46	0.79	90	60	150	152	435	Toxic jaundice	
4.94	1.25	0.25	82	59	141	106	450	Toxic jaundice and furunculosis	Confined to hospital ward
4.48	3.28	0.73	90	60	150	152	435	Toxic jaundice	
9.47	0.27	0.03	95	9	104	124	282	Toxic jaundice	
9.72	0.36	0.04	95	34	129	126	380	Toxic jaundice	
2.22	0.44	0.20	90	60	150	152	435	Toxic jaundice	
4.62	10.22	2.21	90	60	150	152	435	Toxic jaundice	Debilitated unrestricted, up and about
1.07	3.04	2.84	90	60	150	152	435	Toxic jaundice and furunculosis	
4.08	2.52	0.63	90	60	150	152	435	Toxic jaundice	
1.66	8.68	1.73	90	60	150	152	435	Toxic jaundice	
11.54	7.35	0.64	90	60	150	152	435	Toxic jaundice and nephritis	
4.53	5.78	1.27	90	60	150	152	435	Toxic jaundice	Confined to hospital ward
16.25	5.31	0.33	123	35	158	147	366	Toxic jaundice and dermatitis	
8.8	4.24	0.48	123	35	158	147	366	Toxic jaundice and dermatitis	
83.28	3.45	0.10	72	53	125	105	392	Toxic jaundice	
2.34	4.75	2.03	98	37	135	132	414	Catarrhal jaundice	
7.68	6.92	0.90	117	33	150	35	386	Toxic jaundice and dermatitis	Confined to hospital ward
3.25	6.35	1.95	124	33	157	147	353	Toxic jaundice and dermatitis	
3.4	5.8	1.70	102	59	161	118	480	Toxic jaundice and dermatitis	
2.7	7.62	2.82	136	52	188	130	438	Catarrhal jaundice	
22.81	16.38	0.71	90	60	150	152	435	Toxic jaundice	
17.55	11.7	0.66	90	60	150	152	435	Toxic jaundice	Debilitated unrestricted, up and about
12.94	7.0	0.54	109	80	189	162	643	Toxic jaundice	
20.44	4.6	0.22	115	80	195	164	643	Toxic jaundice	
1.45	1.86	1.28	90	60	150	152	435	Bronchitis	
1.33	5.06	3.80	90	60	150	152	435	Disordered action of the heart	
8.14	4.92	0.56	90	60	150	152	435	Meningitis	Debilitated unrestricted, up and about
2.47	5.98	1.15	90	60	150	152	435	General debility	
5.2	11.90	4.84	90	60	150	152	435	Syphilis and tonsillitis	
10.92	4.62	0.42	90	60	150	152	435	Constipation	
0.53	1.18	2.23	90	60	150	152	435	Influenza	Recovered unrestricted, up and about
1.06	1.12	1.06	90	60	150	152	435	Arthritis	
1.41	2.4	1.70	90	60	150	152	435	Gastritis	
1.17	2.68	2.29	90	60	150	152	435	Normal	
1.7	3.12	1.83	90	60	150	152	435	Sclerema	
1.19	1.93	1.62	98	53	151	133	429	Normal	

increase in blood creatinin and uric acid and a decreased excretion of uric acid as shown by the ratio of excretion to blood concentration. These patients were all more or less debilitated and their high protein diet probably accounts for most of the urea nitrogen increase. Unfortunately, the excretion of urea was not estimated.

*Uric Acid*—The relationship between the concentration of uric acid in the blood and the rate of excretion (mg per hundred c c of blood divided by mg per hour excreted) is of interest in considering the blood uric acid. It has frequently been demonstrated that uric acid is the most difficult of the nitrogenous waste products to eliminate and that one of the first signs of failing kidney function is an increase of this substance in the blood.<sup>23</sup> Accepting 3 mg per hundred c c of blood as being the normal upper limit, we find that in 67 per cent of the first twenty-eight cases abnormally high blood uric acid was noted. In only 14 per cent of these cases did we find a uric acid excretion index above 0.2 (Watanabe's figure of slightly impaired kidney function<sup>24</sup>), and in many cases (Nos. 15, 17, 21 and 25) we found a very free excretion associated with a high concentration in the blood, pointing to an increased production of uric acid. As the diet was low in purins and none of these patients had a leukocytosis at the time of examination, one naturally thinks of liver nuclear substance as the source of this uric acid.

TABLE 3

Case	Urobilinogen	Urobilin	Combined Excretion	Relative Oxidation of Urobilinogen	Blood Cholesterol per Cent
Liver cases having bile pigment in plasma—9, 11, 19 to 21, 23 to 28	12.5	7.16	19.66	57	0.238
Improved liver cases, no bile pigment in plasma—2 to 8, 10, 12 to 18, 22	5.34	3.26	8.6	61	0.224
Debilitated cases, not associated with disordered liver—29 to 34	4.92	5.68	10.6	115	0.156
Recovered cases not associated with disordered liver—35 to 40	1.18	2.07	3.25	175	0.154

*Effect of Exercise*—The deleterious effect of exercise on debilitated patients is well shown in Table 4. In the first group, constituting the more serious cases, the urea nitrogen is practically normal, so also the creatinin. There is a slight increase in blood uric acid, but the excretion is very good. These patients were confined to their wards. The second group is made up of patients who had apparently recovered. The diet of this group is 4 per cent richer in protein, but the

<sup>23</sup> Myers, V. C., Fine, M. S., and Lough, W. G. *Arch. Int. Med.* **17**: 570 (May) 1916. Baumann, L., Hansmann, C. H., Davis, A. C., and Stevens, F. A. *Arch. Int. Med.* **24**: 70 (July) 1919.

<sup>24</sup> Watanabe, C. K. *Am. J. M. Sc.* **154**: 76, 1917.

blood analyses show 57 per cent more urea nitrogen, 92 per cent more uric acid, 37 per cent more creatinin, and a little more than one-half the ability to excrete uric acid as shown by the index, these patients, being apparently well, were unrestrained. Reference will be made later to the association of glycogen in the liver with a protection of that organ against poisonous substances. It may be stated, however, that the susceptibility of the liver to the destructive action of circulating toxins is in inverse proportion to the amount of glycogen contained in that organ. Hammarsten and Hedin<sup>25</sup> point out the fact that, during rest, the glycogen content of the liver is greatly increased, and that it is diminished during work. In dogs, Kulz found the liver glycogen reduced to a minimum after a period of a few hours hard work. Considering this with the results shown in Table 4, we see that in the debilitated patients the effect of exercise is to decrease the excretory power of the kidneys, increase the waste products in the blood, and lower the resistance of the liver to toxins.

TABLE 4

Cases	Blood			Index of Uric Acid Excretion*	Protein in Diet		
	Uric Acid, Mg per 100 Cc of Blood	Urea N, Mg per 100 Cc of Blood	Creatinin, Mg per 100 Cc of Blood		Animal, Gm per Day	Vegetable, Gm per Day	Total, Gm per Day
Liver cases, confined to hospital ward—6 to 10 17 to 28	3.57	21.0	1.87	0.064	98	46	144
Liver cases, debilitated, unrestricted up and about—1 to 5 11 to 16	3.9	33.0	2.57	0.121	90	60	150
Debilitated cases, not associated with disordered liver, up and about—29 to 34	4.37	40.5	2.02	0.077	90	60	150
Recovered cases, not associated with disordered liver, up and about—35 to 40	3.05	18.5	2.1	0.086	91	59	150

\* Milligrams per 100 Cc of blood divided by milligrams per hour excreted

In this type of poisoning, decreased oxidative activity has been held accountable for the free autolysis occurring in the liver<sup>26</sup>. Our figures indicate an increased oxidative activity during absolute rest and are a further plea for rest during the treatment of these patients.

A possible explanation of the "delay" in poisoning by arsenobenzol, chloroform, etc., presents itself. Harrison<sup>1</sup> suggests that each dose of arsphenamin contributes its quota of damage to the liver, and that a final dose precipitates the toxic symptoms. In many cases, however, the toxic symptoms do not appear for weeks after the last treatment. It seems quite possible that in these cases the damaged organs are

<sup>25</sup> Hammarsten and Hedin. *Physiological Chemistry*, London and New York 1915 p 391

<sup>26</sup> Wells H G. *J A M A* 46:341 (Feb 3) 1906

able to functionate during the course of treatment, when dietetic and physical restrictions are imposed, but when these are removed, and the patient returns to work and an unrestricted diet, the straw "which breaks the camel's back" has been added and toxic symptoms appear. This is well illustrated in Case 19. The patient had received 4.05 gm of novarsenobillon in seven weekly doses, during the treatment, and for the following three weeks, he remained in the hospital and had no toxic symptoms. He was given seven days leave, however, and returned toxic and jaundiced. Similar observations were made in the case of another patient (Case 8). Assurances were given by each of these men that their lives were abstemious during their absence.

*Clinical Application*—From the above results it would seem that, in addition to considering the protein intake of these patients, we must carefully regulate their exercise. Physical examination fails us in classifying these cases and resort must be had to some functional test if we are to avoid toxic symptoms. In Table 4 the index of uric acid excretion appears to be the best test, but the labor entailed tends to preclude it as a routine method. The estimation of the urea in the blood is the second choice, and its routine use in institutional treatment is quite practicable. An abnormally high value in a patient at rest would be an indication for reducing the protein in the diet, while similar results in "up patients" would, perhaps, call for both rest and protein restriction.

*Diet in the Treatment of Syphilis*—Experimental toxic jaundice has added greatly to our knowledge of liver damage and repair. The lesions produced in the liver by arsenobenzol derivatives are similar to those produced by chloroform and phosphorus, being essentially a fatty infiltration, with more or less necrosis of the liver cells. Opie and Alford<sup>27</sup> have shown that in both chloroform and phosphorus poisoning, less damage is done to the liver if a carbohydrate diet is given. Graham<sup>28</sup> demonstrated that in dogs the resistance of the liver to chloroform is proportional to the amount of glycogen in that organ. Rettig<sup>29</sup> has made similar observations in connection with phosphorus poisoning.

Many interesting and practical observations, which might well be applied to the toxic cases under discussion, have been made by Davis and Whipple<sup>30</sup> from their experiments on liver destruction and repair in dogs poisoned by chloroform. Their findings may be summarized as follows: (1) In starvation, a maximal injury to the liver is to be

27 Opie, E. L., and Alford, L. B. *J. A. M. A.* **62**: 295 (Jan. 24) 1914.

28 Graham, E. A. *J. Exper. Med.* **21**: 185, 1915.

29 Rettig, H. *Arch. f. exp. Path. u. Pharmacol.* **76**: 345, 1914.

30 Davis, N. C., and Whipple, G. H. *Arch. Int. Med.* **23**: 612 (May) 1919.

expected (2) Sugar and diets rich in carbohydrates, fed in the days preceding chloroform anesthesia, exert a marked protective action against liver injury (3) Fats alone, or combinations of food containing fat in large proportion, induce a maximal susceptibility to liver injury (4) Skim milk alone is highly protective (5) A diet of bread and skim milk or any rich carbohydrate diet gives the optimum liver repair (6) A diet of cooked skeletal muscle is not favorable for rapid liver repair (7) Fat diets do not aid in liver repair

Lusk<sup>31</sup> has shown that, in phosphorus poisoning, when the body carbohydrates are lowered, protein metabolism is greatly increased. This is explained by Luthje<sup>32</sup> and Cathcart<sup>33</sup> who conclude that carbohydrates are necessary in the synthesis of protein from the absorbed products of protein digestion. A rich carbohydrate diet would, therefore, ensure a complete assimilation of the protein and call for but a minimum protein intake. In determining this minimum, many factors come into play, these have been considered carefully and applied by Chace and Rose<sup>34</sup> in their dietetic treatment of nephritis. These authors find that 60 gm of mixed animal and vegetable protein is quite sufficient for patients under treatment, provided the necessary carbohydrate is given to make up their fuel requirements.

It would seem advisable in the treatment of syphilis to institute a rich carbohydrate diet very low in fat and protein. This diet should precede the treatment by several days and should be continued throughout its full course. The high blood urea and the prolonged convalescence in our reported cases emphasize the advisability of such a diet being used.

#### SUMMARY

A report is made on the chemical blood and urine analyses in twenty-five cases of toxic jaundice following combined arsenical and mercurial treatment for syphilis, on two cases of catarrhal jaundice, on one case of syphilitic hepatitis, and on twelve cases in which patients were recovering from illnesses not associated with the liver.

Arsenic tests were made on the morning urines at periods ranging from 24 to 157 days after the last treatment and none was found. The twenty-four-hour urines were normal, excepting for pathologic pigments in some of the cases.

Patients clinically jaundiced had bile pigment in their urine. Bilirubin estimations in the plasma, according to Blankenhorn's dilution method, compared favorably with Gmelin's tests and the clinical findings.

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31 Lusk, Graham. *Am J Physiol* **1** 5, 1898

32 Luthje, H. *Arch ges Physiol* **113** 547, 1906

33 Cathcart, E. P. *J Physiol* **39** 311, 1909

34 Chace, A. F., and Rose, A. R. *J A M A* **69**:440 (Aug 11) 1917



Of the liver cases, those patients with bilirubin in the plasma excreted more than twice as much urobilinogen as did those patients who were free from jaundice, the nonjaundiced liver patients excreted more than twice as much as the well persons. Of the cases not associated with disordered livers, the debilitated patients had more than twice the urobilinogen excretion of the well persons.

In the twenty-eight liver cases, the rate of excretion of urobilinogen was one third greater in the early morning than was the average rate during the day.

In the urines, the relative oxidation of urobilinogen to urobilin was greatest in the well persons, less in the debilitated persons, about one third as much in the nonjaundiced liver patients, and still less in the jaundiced liver patients. The relative oxidation was greater in the early morning than in the twenty-four-hour specimens.

The patients with toxic jaundice had a marked increase in blood cholesterol, the jaundiced patients (being also the severe cases) had the greatest increase. In the cases not associated with liver disturbance the cholesterol value was normal.

Sugar estimations in blood and urine revealed no disorder of carbohydrate metabolism.

Blood creatinin estimations showed no marked departure from the normal. Uric acid estimations in the blood and urine indicated an increased production of this substance.

The values for urea nitrogen are normal in the well persons. Of the remaining cases, some patients show normal values, but the majority are above normal. This seems to be due to the high protein diet and deficient physical restrictions placed on these men.

The effect of exercise on debilitated patients seems to decrease the excretory power of the kidneys, increase the waste products in the blood, and lower the resistance of the liver to toxins. This, associated with an increase in the diet proteins, is given as an explanation of the "delay" in poisoning by arsenobenzol, chloroform, etc. Arguments are advanced for the adoption of a diet rich in carbohydrate and very low in fat and protein in the treatment of syphilis.

#### CONCLUSIONS

1 In patients whose livers are damaged by arsenobenzol derivatives, an increase of cholesterol in the blood is an early and marked sign, it persists after other clinical signs have disappeared, its routine estimation may be of value in detecting the onset of liver injury in patients under antisyphilitic treatment.

2 In debilitated patients, the oxidative activity of the urine is decreased. This decrease is much more marked if the liver is disordered. In such cases the oxidative activity is greatest during absolute rest.

3 Exercise should be restricted greatly during the course of anti-syphilitic treatment and for the following few weeks.

4 A diet, rich in carbohydrate and very low in fat and protein, should precede, accompany and succeed the administration of arseno-benzol derivatives in the treatment of syphilis.

5 Increase of protein in the diet, and of exercise, should be controlled by the estimation of the urea in the blood.

6 The appearance of toxic symptoms in delayed poisoning by arsenic, phosphorus, chloroform, etc., is possibly due to the premature increase of protein in the diet, and of exercise in these cases.

We wish to thank Lieut-Col C F Martin, Lieut-Col G S Strathy, Major Wallace Wilson, Major W H Tytler and Capt Beverley Hannah of the C A M C, for expediting this work, and Prof E P Cathcart and Dr G H Paul for suggestions in the preparation of the manuscript.

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## A CASE OF HEREDITARY DIABETES \*

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As the cause of hereditary or familial diabetes is of interest for the subjects of both diabetes and heredity, the opportunity was taken of making some observations concerning it in one case on the diabetic service of this hospital

### REPORT OF CASE

*Family History*—The family are "poor whites" in a little mountain hamlet of South Carolina, and offer three features of special interest for a study of heredity. First, is the isolation of the community, the absence of immigration, and the thorough knowledge concerning their ancestry and relatives for several generations back. Second, is the large size of the family, and the remarkably high incidence of diabetes encountered in one generation. Third, is the fact that before his marriage to the mother of the present family of children, the father had had an illegitimate child by another woman, which developed diabetes, though that woman and her family were free from diabetes. This, and the diabetes in the father's brother, indicated that the diabetic heredity came through the father.

*Personal History*—Mumps, measles, chickenpox, whooping cough and smallpox before the age of 10 years. Otherwise healthy, lived the usual life of the family, doing mostly farm labor. Rather thin and undernourished like the others, no dietary excesses, no alcohol, moderate tobacco. No trauma. Venereal disease or exposure denied.

*Present Illness*—In 1915 there appeared polydipsia and polyuria without polyphagia or other symptoms. Sugar was found in the urine, and the diagnosis made promptly, but the patient continued at work without dietary restriction, feeling well notwithstanding continuous glycosuria. Cough began in 1915 and continued thereafter but was not regarded as serious. Fistula in ano in November, 1917. In April, 1918, the patient was drafted, sent to a camp, examined and passed. He said nothing about his diabetes and cough for fear of appearing unpatriotic. He performed the regular duties of his company, which happened to be light and was sent overseas in August. In England he had to fall out on a three mile "hike" because of backache and weakness, but was transported to France and did full duty for three months, till hard marching was begun and he again had to fall out. He was sent to a field hospital for supposed heart trouble, where the diagnosis was made but no dietetic treatment given. There was rapid progressive loss of weight, and he was shipped for America in bedridden condition in October, 1918. The ship doctor instituted carbohydrate-free diet as far as possible, and the patient improved enough during the trip to walk a little. After landing, he was on ordinary mixed rations for two weeks, and was admitted to this hospital, October 30, on a stretcher in critical condition from both weakness and acidosis.

*Physical Examination*—Extremely weak and emaciated patient in early stage of coma, but able when roused to answer questions. Temperature, 99 F, pulse, 120, respiration, 24, blood pressure, 105/75, height, 5 feet 11 inches, weight, normally, 70 kg now 47 kg. Teeth in very bad condition with caries.

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\* From the Diabetic Service, U S Army General Hospital, No 9, Lakewood N J

and pyorrhea, one root abscess. Signs of consolidation in apices of both lungs, extending half-way down on right side. Slight general lymph gland enlargement. Knee jerks absent. Marked myotonia reaction in muscles. Other findings negative.

*Laboratory*—Sputum abundant, gray, mucopurulent, thick, but containing no tubercle bacilli or elastic tissue. Urine albumin negative, acetone and diacetic heavy, sugar 130.6 gm for twenty-four hours of October 31. Blood plasma sugar, 0.850 per cent, nitroprussid, very heavy, carbon dioxide capacity, 23.6 volume per cent.

*Treatment and Progress*—The patient entered in the late afternoon, and received only soup and water to capacity. By the next morning his condition was about the same, though the carbon dioxide capacity had fallen to 21.4 volume per cent. Fasting seemed safe from the standpoint of acidosis, but in view of the serious weakness and tuberculosis, a fat-free diet was begun, of 125 gm carbohydrate and 100 gm protein, diminishing gradually to 25 gm carbohydrate and 70 gm protein November 4. No alkali or alcohol was given. The urinary sugar fell to 4.6 gm and the plasma sugar to 0.5 per cent, the carbon dioxide capacity rose to 29 volume per cent, and the general condition was much improved. Continuous fasting was then necessary from November 5 to 11 inclusive, to abolish glycosuria. The plasma sugar fell to 0.189 per cent, the carbon dioxide capacity rose to 40 volume per cent, and the nitroprussid reaction almost disappeared from the plasma and urine. It is noteworthy that during this time the patient's strength increased greatly, and the cough and sputum markedly diminished. When it was attempted to give a fat-free diet of 25 gm protein and 5 gm carbohydrate, glycosuria promptly returned. In order to bring down the blood sugar and build up tolerance, a three-day fast was imposed, followed by a diet of nothing but 20 gm protein, increased gradually to 60 gm November 24. The plasma sugar was then brought to 0.105 per cent November 30, while all signs of acidosis were absent, and the plasma carbon dioxide remained continuously at a high normal level (60 to 70 volume per cent) thereafter. Ten gm carbohydrate was then added, with fat to raise the total calories to 800. With a gradual increase, broken by occasional single fast-days, by December 19 the patient was taking 80 gm protein and 50 gm carbohydrate, a total of 1,200 calories. Owing to a tendency to slight hyperglycemia, the carbohydrate was reduced to 30 gm January 7.

About this time was the stage of maximal improvement lasting about two months. The patient walked to town daily and spent much of each day in the open air. His hunger was fairly well satisfied by a bulky diet, and he took some real pleasure in life. The lowest weight during the rigorous undernutrition was 46 kg. Subsequently, there was a rise as high as 48.6 kg. Invisible water retention is a possible element in such a gain. Continued improvement was impossible in the presence of two factors, one, the tuberculosis, which was at a hopeless stage even for a non-diabetic, the other the patient's ignorance and unreliability so that he began to break diet frequently as he felt better. In February, on this account the diet was raised to 1,500 calories, though hyperglycemia, without glycosuria but with traces of nitroprussid reactions, was the necessary result.

During this optimum period the cough and other symptoms of tuberculosis were almost absent, but physical examination indicated a steady advance of the process. Gradually, subacute attacks of cough and pleuritic pain came, lasting a few days each time. Later a moderate pleural effusion appeared on the left side, 10 cc of fluid withdrawn with a syringe was clear, sterile, poor in cells and contained 0.178 per cent sugar. Sputum examinations remained negative until April 5, after which tubercle bacilli were constantly present.

During the entire time special attention was paid to the question of possible syphilis. Wassermann tests of the blood and spinal fluid in this hospital by Capt Cyrus Field and Lieut J W Sherrill, with various combinations of serum and antigens were negative. Inactivated serum sent to St

## ANALYSIS OF HEREDITARY FACTORS IN THIS CASE

Persons	Height	Weight	Complexion	Hair	Eyes	Death		Living Age	Wassermann	Dose of Glucose Gm	Glucose Tolerance Test				
						Age	Cause				Before	1/2 Hr After	1 Hr After	2 Hrs After	3 Hrs After
Father's father	Similar to father	Similar to father	Light	Flaxen	Blue	Advanced	Apoplexy								
Father's mother	Similar to father	Similar to father	Dark	Black	Black	Advanced									
Father	5 ft 9 in	115-150 max	Dark	Black	Blue	Middle life	One from her side, the other from diabetes								
Two brothers of father	Similar	Similar	Dark	Black	Blue										
Three sisters of father	A little shorter	Never obese	Dark	Black	Blue			Well at advanced age							
Mother of illegitimate child	5 ft 10 in	Medium or thin	Light	Flaxen	Blue	Unknown									
Illegitimate child (born 8 or 9 years before marriage)	5 ft 10 in	Medium of thin	Light	Flaxen	Blue	35	Diabetes several years duration								
Mother's father (also his brothers)	6 ft 2 in	Not obese	Light	Flaxen, red beard	Blue	Advanced									
Mother's mother	Tall nearly 6 ft	Not obese	Dark	Dark	Dark	Advanced									
Mother of present child	5 ft 5 1/2 in	130	Light	Flaxen	Blue	Advanced age or still living		55	Negative	100	0 113	0 142	0 142	0 142	0 106
Fourteen brothers and sisters of mother	Women tall, men over 6 ft	Not obese	Light	Flaxen	Blue										
Present Children															
1st, a girl	5 ft 8 in	Medium	Light	Flaxen	Blue	12	Diabetes duration only 5 months								
2d, a girl		Medium	Dark	Black	Blue	26	Diabetes duration only 3 years								
3d, a girl	5 ft 4 in	Medium	Dark	Black	Blue	32		32, has one healthy child female, 5 yrs	Negative	100	0 166 *0 133	0 250 0 217	0 289 0 205	0 166 0 144	0 094 0 089
4th, a boy	5 ft 10 in	147	Dark	Black	Blue										
5th, a girl		Medium	Dark	Black	Blue	10	Diabetes duration only 2 or 3 months								
6th, a boy	6 ft	Medium	Light	Flaxen	Blue	1 month	Unknown	25, 6 years in U S Army	Negative	100	0 123	0 192	0 156	0 125	0 091
7th, a boy	5 ft 11 in	153	Light	Brown	Blue			23, diabetes known since 1919	Negative in blood and spinal fluid						
8th, present patient			Light	Flaxen	Blue			19, well	Negative						
9th, a girl	5 ft 7 1/2 in	130	Light	Flaxen	Blue			16, well	Negative	100	0 123	0 200	0 151	0 109	0 099
10th, a boy	Tall	Thin	Medium	Flaxen	Blue			14, well	Negative	75	0 114	0 143	0 143	0 102	0 099
11th, a boy	Tall	Thin	Dark	Black	Blue				Negative	50	0 107	0 127	0 127	0 116	0 102
12th, a boy	Medium	Thin, sleekly	Medium	Brown	Blue	9	Diabetes, duration 3 months								
13th, a boy	Medium	Medium	Light	Flaxen	Blue			9, well							
											Refused blood test without glycosuria				
											Took 75 gm glucose				

\* The lower row of figures represent the sugar percentages in whole blood

Luke's Hospital, New York, was reported negative by Dr L W Famulener, also a sample sent to the Peter Bent Brigham Hospital, Boston, was found negative by Dr Charles Walker. Serum and spinal fluid were both reported negative by the Army Medical School, Washington, and by Dr B A Thomas of the Philadelphia Polyclinic, the latter mentioning the use of syphilitic, cholesterinized and acetone insoluble lipid antigens. The only exceptional findings were a single positive reaction in the serum obtained by Lieut H T Hyman in this hospital, who in an immediate repetition failed to confirm it, and a positive report by Dr C C Warden of Ann Arbor, Mich, who used a special modified method. The globulin test and cell count of the spinal fluid were normal. Careful examinations by the medical and genito-urinary staffs revealed no signs of either acquired or hereditary syphilis, and likewise nothing suspicious was found in specialized dental and nose and throat examinations. Clinical and Wassermann examinations were also uniformly negative in the other individuals of the family as shown in the table.

Acknowledgement is due to the local Red Cross for paying the expenses of several visits by the relatives, which not only were a great comfort to them and the patient but also afforded the opportunity of extending the investigation to all members of the family.

As the tuberculosis became the dominant element in the condition, the diet was slightly relaxed and fast-days omitted, but the average of total calories was always kept below 2,000, not on account of any diabetic danger, but in order to avoid the great lowering of resistance which results from unchecked diabetes. Glycosuria was permitted occasionally during March, and constantly during April. The lowest weight was 44 kg without edema, indicating that the emaciation had been controlled better than by the usual over-feeding program. May 9 the patient went into what seemed to be normal sleep, and died apparently from weakness within two hours. The blood plasma analyses are shown in Table 2.

TABLE 2—BLOOD PLASMA ANALYSES ON THE FINAL DAYS

Date	Sugar, per Cent	Nitroprussid	CO <sub>2</sub> Capac- ity, Volume per Cent
May 4	0.484	Heavy	57.9
May 5	0.555	Heavy	55.1
May 6	0.517	Moderate	62.3
May 7	0.600	Slight	
May 8	0.405	Faint	70.0
May 9	0.041	Negative	76.7

The clearing of sugar and acetone was not explainable by the diet as the patient ate and apparently digested 60 gm protein, 20 gm carbohydrate and 1,800 calories regularly up to the day of death. It did not indicate improvement in the diabetes, but was evidently a terminal phenomenon of exhaustion such as is familiar in dogs. The fact that dogs with severe phloridzin or diabetic acidosis may become free from acetone bodies at the end is one argument against these substances as the cause of death. Malnutrition and tubercular intoxication furnish sufficient reasons for death in the present case, without the necessity of assuming any unknown causes of coma.

#### NECROPSY

The necropsy was performed immediately, as necessary for the proper study of diabetic pathology. The gross necropsy was performed by Lieut J W Sherrill.

Both pleural membranes were greatly thickened and adherent, except at the bases, where there was about 300 cc of clear fluid on each side. The lungs were mostly air-containing without massive consolidation, but cavi-

ties ranging in size from a pea to a walnut, with well formed walls and full of thick yellow pus, were scattered throughout both, and they were also riddled with small solid tubercles of pinhead to pea size. The abdomen contained about 300 cc clear fluid and very little fat. The mesenteric glands were rather prominent but not caseated. The liver weighed 1,200 gm and was normal and free from visible tubercles. The gall bladder contained about 50 cc clear yellow bile and appeared normal. The spleen weighed 125 gm and contained no visible tubercles or changes in parenchyma. The pancreas was pale, but normal in size, shape and consistency.<sup>1</sup> The kidneys together weighed 300 gm and appeared normal throughout. Stomach, intestine, adrenals and testicles normal. The skull was not opened.

*Microscopic Examinations*—Specimens of the tissues in absolutely fresh condition were taken in formaldehyd and in Zenker solutions, and were sent to Dr J Ewing, New York, Dr F B Mallory, Boston, and Dr A S Warthin, Ann Arbor, to whom thanks are due for their courtesy in studying the material. Professor Warthin's report on the organs in general is summarized as follows:

**Liver** Brown atrophy, passive congestion, very young miliary tubercles, small celled infiltration of some of the islands of Glisson.

**Gallbladder** Chronic catarrhal cholecystitis, slight.

**Kidneys** Congestion, cloudy swelling, no glycogen vacuolation of the loops of Henle.

**Retroperitoneal Lymph Nodes** Chronic lymphadenitis, numerous miliary tubercles. In the hilum of the lymph glands and through the retroperitoneal fat many xanthelasma cells. Some of the primitive fat lobules completely converted into a lobular organ of these. The ordinary fat tissue shows marked serous atrophy with proliferation of the endothelial and stroma cells.

**Spleen** Marked congestion, atrophy of the lymphoid tissue, stroma is increased and there is an endothelial cell proliferation in the sinusoidal spaces. Some of these cells show vacuolation.

**Lungs** Congestion, edema, atelectatic and emphysematous areas, one young tubercle.

**Bronchial Nodes** Contain many miliary tubercles.

**Suprarenals** Hypoplasia of the medulla and lipoidosis of the cortex.

**Testes** Simple atrophy, no orchitis.

**Heart Muscle** Simple atrophy and fatty infiltration, serous atrophy of the fat, no myocarditis, fatty degeneration.

No evidences of syphilis.

All Levaditi preparations negative.

Specimens of the aorta were unfortunately omitted from the tissues sent to Dr Warthin, but were included among those sent to the others. All three pathologists were agreed concerning the complete absence of syphilitic changes in all viscera.

The pancreas calls for special notice. A report was received from Warthin, three slides from Mallory and two from Ewing. The general appearance was more or less atrophic. The acini were mostly small, shrunken and nearly empty, but the acinar arrangement was always preserved, a little zymogen was everywhere present, and there was nowhere any actual involution. These appearances belong merely to inanition. They were mentioned by Warthin, and present in marked degree in Ewing's slides, while in Mallory's slides the zymogen was more abundant and the acini practically normal. Warthin also mentioned some dilated and some hypertrophic acini. Where the acini were shrunken the fibrous elements as usual were relatively more prominent, but there was no definite fibrosis found in the acinar tissue. The following features of the islands may be noted. *Number*—Fewness of islands was men-

<sup>1</sup> Removal of the pancreas was the first step in the necropsy, and weighing of it was omitted in the interests of quick fixation.

tioned by Warthin, and they were noticeably few and small in four of the five slides mentioned. In one slide from Mallory islands were fairly abundant and a few were so large and irregular as to suggest hypertrophy. There was nowhere seen any such scarcity as to suggest congenital deficiency of island tissue as the cause of the diabetes. (b) *Fibrous and hyalin changes*—None such were mentioned by Warthin or Mallory, or observed in the Mallory slides. Ewing's slides showed slight distinct fibrous thickening of the capillary network of all islands, with small hyalin deposits in many of them. (c) *Weichselbaum's "atrophy"*—This was not mentioned by Warthin or Mallory, and the island cells appeared normal in the slides received from Mallory. In Ewing's slides the cells in the great majority of the islands appeared abnormally small, with dense and shrunken cytoplasm and nuclei. This change may have been specific and significant in this instance, along with the slight fibrosis of islands, or may merely have been part of the atrophic appearance of the general parenchyma. (d) *Hydropic degeneration*—No vacuolation of islands was reported by Warthin, though he mentioned it in tissue from another case sent at the same time. None was found in Mallory's slides or in the great majority of islands in Ewing's slides. But a few islands in the latter were composed almost wholly of swollen cells showing the typical hydropic vacuolation in marked degree.

#### DISCUSSION

Incidental mention may be made of the treatment and its results. Obviously, the combination of advanced diabetes and advanced tuberculosis was hopeless. The outstanding fact is the marked improvement in the tuberculosis as well as the diabetes under diet treatment, even though this involved undernutrition. In this extreme condition, complete fasting was imposed for a week, followed by very low diets chiefly of protein, so that over a month was occupied in a gradual increase up to 1,200 calories. Gain in strength and resistance to infection was evident during this time. Life was extended for six months. As a lesson for the treatment of milder tuberculosis or prophylaxis against it and other infections in diabetics, the experience indicates that the best success will be attained with restricted diets which control the diabetes, rather than by attempts at over-feeding. It also corroborates other observations that thoroughly treated patients not only live longer but are at the same time more comfortable.

The principal feature of interest is the diabetic heredity. The frequent occurrence of diabetes in certain families is well known, generally as a more or less heavy sprinkling of cases through several generations, but sometimes apparently as a sudden visitation on a single generation out of a clear heredity. Examples are cited in Joslin's and earlier textbooks, and two cases and a bibliography is given in a paper by Foster.<sup>2</sup> The newer ideas of the usual infectious origin of diabetes makes it probable that some cases are strictly accidental and without hereditary influence. Therefore, in addition to the great theoretical interest, there is much practical importance in this point with reference to the frequent question whether diabetics should marry or have chil-

<sup>2</sup> Foster, N. B. Bull. Johns Hopkins Hosp. 23: 54, 1912.



dren For a fuller discussion and outline of other investigations by one of the present writers, reference may be made to Chapter 8 in Rockefeller Institute Monograph No 11 The observations in the present case may be classified as they pertain to hereditary characters, the pathology, and infections

1 *Heredity*—(a) General conditions The table shows the ancestry beginning with the grandparents of the present children In the light of their experience with diabetic symptoms, the mother and older children were positive from diligent inquiries among all their oldest relatives that nothing of the sort had been known in the family up to this time The first known case was in a brother of the father The death of the father from apoplexy may indicate nephritis, but this at the age of 61 may carry no great significance As the family were very ignorant, the occurrence of mild diabetes or other organic diseases among some of the ancestors in their later years is not fully excluded, but the testimony goes far to exclude any severe or obvious diabetes and to establish long life and health as the rule among them There was no history of inbreeding It may be added that obesity, sedentary life, high civilization and education, nervous strain and similar reputed causes of diabetes were unknown among them, also their diet was frugal and simple, containing little sugar, fair quantities of cornmeal and wheat flour, adequately balanced with meat and vegetables from their own farms

(b) Accompanying characters The grandparents on both sides represented a combination of light and dark individuals The pure blond character of the maternal grandfather was dominant over the brunet color of his wife Both these grandparents were notably tall, but the mother of the present children was exceptional among her brothers and sisters for her shortness The colors of the paternal grandparents blended to produce offspring characterized uniformly by black hair, dark complexions and blue eyes The first known case of diabetes occurred among this generation of mixed coloring The father of the present children was taller than the mother, but his family averaged shorter than the mother's family

Little concerning the heredity of the present children can be elucidated from their height Four of the diabetic children (No 2, 3, 4, 5) resembled the father in being blue eyed brunets One such child (No 11) has thus far escaped diabetes, according to his glucose test The illegitimate child was a pure blond like his mother, but nevertheless became diabetic Two of the present children were classifiable as blonds like their mother except for their hair, which showed a partial influence of the father in being brown To date, the children having full resemblance to this mother, including her flaxen hair (Nos 1, 7, 9,

10, 13) have been free from known diabetes. Every rule of association of diabetes with other characters, therefore, has exceptions, though it can be said that all of the legitimate children who most closely resembled their mother have escaped diabetes. Also, in general, the father's influence was most pronounced among the earlier children, and these up to No 6 (except No 1, who died at 12 years from a fall) all developed diabetes. The later children showed less influence from the father in general and correspondingly less diabetes. As the father was about ten years older than the mother, there may be a question whether advancing age had anything to do with his loss of dominance.

(c) Unit inheritance. The above record shows certain characters of complexion, etc., sometimes transmitted as units and sometimes more or less blended. It may be inquired whether the diabetic disposition behaved as a mendelian unit or was blended so as to produce varying grades of carbohydrate tolerance. This bears relation to the practical question whether all children of a diabetic family observe precautions in diet or whether some may enjoy the liberty of normal persons. It is clinically well known that some members of diabetic families do indulge in unlimited gluttony and still escape diabetes, but it is not established whether the danger from such practices is greater to them than to other persons. The glucose tolerance tests revealed one case of incipient diabetes in this family (No 4), and this individual received the benefit of early instructions in dietary care. It is an open question how early in his life the test would have indicated such an abnormality, whether the diabetic tendency was congenital or began with a pancreatitis. Of the two tests taken at the half-hour interval after the dose (Nos 7 and 9), it is noticeable that both show distinctly high values (0.192 and 0.200 per cent), but general experience by no means justifies the suspicion of diabetes in persons showing such figures when the results in the subsequent samples are normal. If there is any diabetic tendency or need for carbohydrate restriction in any of the children other than No 4, these tests do not reveal it. Two facts from animal experiments merit consideration in this connection. First, the proportion of pancreas which must be removed to cause diabetes varies from about seven-eighths or nine-tenths in the dog to about four-fifths in the cat, and very large fractions, fully two-thirds in the dog, must be removed to produce any demonstrable lowering of carbohydrate tolerance. The margin of safety in the human pancreas is unknown, but is presumably large, so that possibly the loss of from one-half to two-thirds of its islands or a corresponding functional deficiency might be undetected in tolerance tests and yet be important as narrowing the margin of safety. The second is that in animals the division point between diabetes and its absence is sharp and definite, and may be represented

by only a fraction of a gram of pancreatic tissue. Up to this point no matter how low the tolerance, the production of diabetes is impossible by carbohydrate excess in any degree or duration. After removal of the additional bit of tissue, though the tolerance may appear little changed, the animal is potentially diabetic and its fate thenceforth is governed by the diet. The deduction from this is that diet may aggravate but never actually produce diabetes, that no matter how narrow the margin of safety, diabetes can result only from some infection or other further injury of the pancreas, and that carbohydrate restriction is unnecessary unless diabetes is already present. In animals, the ready assimilation of sufficiently large quantities of sugar suffices to demonstrate the absence of diabetes and the harmlessness of carbohydrate feeding, but in them the pancreatic islands are normal in character and only artificially reduced in quantity. The pathology of human diabetes as far as now known is against such a simple quantitative explanation and requires the assumption of functional defects in the islands. It is therefore not possible to say with certainty that the normal outcome of a glucose tolerance test proves that the pancreas of an hereditarily predisposed individual can carry a heavy burden on its endocrine function indefinitely without breaking down.

**2 Pathology**—(a) **Methods** Simple methods, namely, Zenker fixation, paraffin sectioning, and staining with eosin and methylene blue or hematoxylin, are sufficient for all purposes except special investigations requiring differentiation of alpha and beta cells in the islands. The reasons why pathologists have generally observed only the structural alterations and missed the finer specific changes described as long ago as 1901 by Weichselbaum,<sup>3</sup> are chiefly two. First is the failure to obtain sufficiently fresh tissue. Immediate necropsy, with removal of the pancreas as the first step, is the best procedure. Though the rate of autolysis varies widely, specimens more than a few hours old are seldom satisfactory. The freshness of animal tissues, where even agonal changes are avoided, is one reason why the changes seen in them are so much more distinct. Second is the failure to study a sufficient number of sections. Specimens should be taken in separate bottles from the different portions of the gland, and a negative report is not justified unless several dozen slides, representing several different blocks from each portion, have been thoroughly searched. The differences found by Bensley<sup>4</sup> even between adjacent areas of normal pancreas are more marked in pathologic material, and the most accurate description of a few slides may be misleading.

<sup>3</sup> Weichselbaum, A., and Stengl, E. *Wien klin Wchnschr* **14** 968 1901, **15** 969, 1902. Weichselbaum, A. *Sitzungsber d kais Akad Wissensch* **119** 73, 1910, *Wien klin Wchnschr* **24** 153, 1911.

<sup>4</sup> Bensley, R. R. *Am J Anat* **12** 297, 1911.

(b) Cellular exhaustion In milder diabetic cases the functional overstrain is seldom rapid and intense enough for positive anatomic demonstration In severe cases with unchecked symptoms, the hydropic degeneration of Weichselbaum and Stangl is seldom missed in a thorough search of fresh material Anyone interested can easily convince himself with animal experiments that this change represents anatomic destruction of island cells by functional overstrain The severest diabetes, if thoroughly controlled by diet, never shows hydropic degeneration, and the strongest argument for thorough treatment is that it actually prevents this form of progressive destruction of islands Less thorough dietetic control gives corresponding anatomic pictures This patient had had moderate glycosuria for some weeks before death, accordingly, visible exhaustion of island cells was not widespread but could be found by search

(c) Structural abnormalities No structural changes of the pancreatic parenchyma have ever been found strictly specific of diabetes, though fibrosis and hyaline transformation of islands are highly suggestive and in their most pronounced grades must entail diabetes The variable pictures in the human pancreas can by sufficient care be duplicated in animal experiments, where an acute aseptic inflammation gives rise to diabetes The production of considerable fibrosis without diabetes is readily comprehensible; but what has not been generally appreciated in clinical pathology is the nearly perfect structural repair which can be attained after an acute pancreatitis has actually caused diabetes Even though the fibrosis or other visible lesions at autopsy be slight, they may assume much importance as vestiges of a former severe inflammation, or on the other hand as evidence of a low grade chronic toxic injury Even a normal pancreatic structure with diabetes could receive a rational interpretation through the above experiments, though as a matter of fact, the extensive clinical series on which these generalizations are based has included no diabetic pancreas actually free from signs of infectious or toxic injury The evidence in the present case is indecisive, because the slight sclerosis of islands might conceivably be due to the toxins of tuberculosis subsequent to the beginning of diabetes Nevertheless, the findings fall within the terms of a previous statement, that the pathology of hereditary diabetes resembles that of diabetic cases in general<sup>5</sup> The evidences of inflammatory or toxic injury are the same, and the problem of heredity is not one of direct transmission of diabetes or anatomic lack of islands, but rather of liability to certain forms of pancreatic injury or the consequences of them

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<sup>5</sup> Rockefeller Institute Monograph No 11 Chapter 8

3 *Infection*—(a) Theoretical status The few early suggestions of diabetes as a communicable disease were baseless, and interest and clearness concerning it as the consequence of infectious injury of an endocrine organ may be said to date from the pronouncement of Woodyatt.<sup>6</sup> Syphilis as a cause of diabetes was especially emphasized by Warthin.<sup>6</sup> Cases of diabetes apparently due to acquired syphilis are known to most clinicians and furnish support for the general conception of the infectious etiology. The clinical evidence for hereditary lues is less definite, but the characteristic pancreatitis of syphilitic fetuses and infants furnishes some presumptive support. Certainly most pancreatitis and most diabetes is not syphilitic. Organisms of the streptococcus group, so strongly stressed by the Rosenow school, are probably responsible for many more cases but it is not proved that they hold any monopoly. The organisms of pneumonia, mumps, typhoid and other diseases, as well as staphylococci and colon bacilli, appear clinically as causes of diabetogenic lesions. It seems reasonable that many such cases are strictly accidental and without hereditary origin or influence.

(b) General diseases The apparently sudden occurrence of diabetes and apoplexy in a certain generation, followed by widespread diabetes in the next generation and especially the transmission through the father to both illegitimate and legitimate offspring, brought this case preeminently under the suspicion of syphilis. Accordingly, this question received attention and it can be said from clinical and blood studies of the family, clinical and Wassermann examinations (blood and spinal fluid) of the patient, and from the gross necropsy, the microscopy of the tissue and stains for spirochetes, that syphilis was absent. Malaria, hookworm and pellagra were also considered and excluded. It is conceivable that one or more of the childhood diseases which this patient passed through might have caused pancreatic injury, especially in a predisposed individual followed by functional deterioration and the outbreak of diabetes years later but such an idea here is merely speculative.

(c) Local diseases. Owing to the excellent efficiency and cooperation of the various services of the hospital, it was possible to have roentgenograms of the patient's teeth and special examinations by the dental, eye, ear, nose and throat, genito-urinary and surgical services in addition to the medical service. Except for dental caries and pyorrhea evidently due to diabetes and neglect, nothing was found which in the opinion of any of the consultants could have served as a focus of infection or intoxication to give rise to the diabetes. The microscopic pathology was discussed above in relation to the etiology through infec-

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6 Woodyatt R. T. Abstract of Proceedings of Seventh Annual Meeting of American Society for Advancement of Clinical Investigation, 1915, p. 25

tious or toxic injury of the pancreas, but no reason was found for the susceptibility of this patient or others of his family to such injury. The bile and pancreatic passages were clear, and the localization of the lesions in the islands suggested an origin not through the ducts, but through the blood stream. Two hypotheses might suggest themselves, namely, that the diabetic predisposition might consist merely in a liability to low grade septicemia or toxemia (which would be convenient to explain the association of diabetes, nephritis and other endocrine disorders in different members of a family), or on the other hand that the slight changes in this pancreas were not primary or etiologic, but purely secondary to the tuberculous and mixed infection of the lungs. The chronic lymphadenitis might harmonize with either of these views, neither of which can be disproved in this case, but the negative findings in most of the viscera here, and the numerous cases of diabetes without other diseases, would seem to indicate a special vulnerability of the endocrine pancreatic structures in this family. Rosenow's theory of a specific and heritable lack of resisting power in certain organs against certain micro-organisms would explain such a condition. Some anatomic peculiarities falling under the more orthodox conceptions of heredity, for example, a circulatory apparatus faulty either structurally (in the vascular supply or the position of the organ) or functionally (through the nerve supply) might predispose to infectious or toxic injury, and the latter assumption might revive the old hypothesis of the nervous etiology. It is only possible at present to state the facts of pancreatic damage in hereditary cases and leave the explanation to the future.<sup>7</sup>

#### SUMMARY AND CONCLUSIONS

1 One of the patients in the diabetic service of this military hospital came of a family in which seven out of fourteen children of one father (one by one woman, thirteen by another woman) were diabetic. In addition to the treatment, clinical and pathologic studies were carried out in the attempt to throw light on the hereditary feature of the condition.

2 The patient when received was in the later stages of diabetes and tuberculosis, with dangerous acidosis, emaciation and weakness. In consequence of a week of fasting and a month of extreme under-nutrition, he became able to tolerate diets between 1,500 and 2,000 calories without glycosuria or acidosis, showed improvement in strength and lung symptoms, and lived six months. This result in a case of this severity adds to the evidence that the combination of diabetes and tuberculosis is best treated by a diet which controls the diabetes.

<sup>7</sup> Warthin, A. S., and Wilson, U. F. *Am. J. M. Sc.* **152**: 157, 1916. Warthin, A. S. *The Harvey Lectures* **13**: 1917-1918.

3 Clinical examinations of the patient and his family for general or focal infections, including clinical and serological examinations for syphilis, were negative. Glucose tolerance tests afforded an early diagnosis of one of the above-mentioned seven cases of diabetes, but were negative in the mother and remaining children.

4 The gross and microscopic pathologic findings served further to exclude syphilis, and were characteristic of tuberculosis. The pancreas showed changes of two types, namely, occasional hydropic degeneration of islands, which is the result of functional over-strain, and slight fibrosis and hyalin formation in islands, which may indicate infectious or toxic damage as the cause of the diabetes.

5 In general, the diabetic heredity, which apparently came through the father, was manifest in the children who most resembled him in coloring of complexion, eyes and hair, but the rule was not absolute. As far as glucose tolerance tests could decide, the diabetic tendency was inherited as a unit character and the tolerance of the remaining children was apparently normal, but this evidence is not decisive, partly because of the limitations of this test in revealing pancreatic deficiency, and partly because the tendency might consist in a susceptibility to infectious or toxic injury, which might yet appear in the other children if the proper organism gained access. This case conforms to the general rule that signs of infectious or toxic damage are found similarly in hereditary and other cases of diabetes. The reason for the peculiar liability to diabetogenic injuries of the pancreas in certain families is undetermined.

# PREVENTION OF SIMPLE GOITER IN MAN

## FOURTH PAPER\*

DAVID MARINE AND O P KIMBALL

CLEVELAND

In previous publications<sup>1</sup> we have outlined the plan of prevention, presented the data of the incidence of thyroid enlargements as determined by annual surveys of all new pupils in the Akron public schools, and the results of the prophylactic use of sodium iodid for nineteen months. The present paper deals with the data obtained at the fourth general examination made October 13-17, 1919, together with summaries and conclusions based on observations extending over a period of thirty months.

### ANALYSIS OF THE RECORDS OF NEW PUPILS

The general data of the clinical condition of the thyroid gland are given in Table 1. For comparison and reference the figures for the three previous examinations are also given.

The pupils included in this table are new admissions to all grades from the fifth to the twelfth, inclusive, and presumably had not previously received iodin. The figures in the first line represent the results of the original survey of all girls in grades from the fifth to the twelfth, inclusive. The figures in the second line include (1) incoming fifth grade girls, (2) girls entering grades above the fifth grade, and (3) girls of two schools that accidentally lost the records of those not taking the treatment. The figures in the third and fourth lines include (1) incoming fifth grade girls and (2) girls entering grades above the fifth. The progressive increase in the percentage of normal thyroids (43.6, 47.0, 55.4 and 65.4) and the corresponding progressive decrease in the percentage of enlarged thyroids whether taken together (56.4, 53.0, 44.6 and 34.5) or as separate groups (slightly enlarged, moderately enlarged and markedly enlarged) are due to the increasing preponderance of fifth grade girls in the second, third and fourth groups. This is also shown in Table 2, where all new pupils are grouped according to ages. Fifth grade pupils average from 10 to 11 years of age, and approxi-

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\* From the Department of Experimental Medicine, Western Reserve University.

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1 Marine, D., and Kimball, O. P. The Prevention of Simple Goiter in Man. *J. Lab. & Clin. Med.* 3:40, 1917. Kimball, O. P., and Marine, D. The Prevention of Simple Goiter in Man (Second paper), *Arch. Int. Med.* 22:41 (July) 1918. Kimball, O. P., Rogoff, J. M., and Marine, D. The Prevention of Simple Goiter in Man (Third paper). *J. A. M. A.* 73:1873 (Dec. 20) 1919.



TABLE 1—ANALYSIS OF THE RECORDS OF NEW PUPILS

Date Examined	Total Cases Examined	Total New Cases	Normal		Slight Enlargements		Moderate Enlargements		Marked Enlargements		Adenomas	
			Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
April 1917	3 872	3 872	1,688	43.6	1 931	49.9	246	6.3	7	0.2	39	1.0
November 1917	4,415	1,772	831	47.0	820	46.2	121	6.8				
November 1918	4 277	1,873	1,037	55.4	779	41.6	53	2.8	4	0.2	6	0.3
October 1919	5 520	2 162	1,415	65.4	679	31.4	67	3.1	1	0.05	1	0.05

TABLE 2—SUMMARY OF AGE INCIDENCE—NEW PUPILS

Date of Examination	Total New Cases	Age									
		10 - 12		12 - 14		14 - 16		16 - 18		18 - 20	
		Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent
April 1917	3 872	945	24.4	1 261	32.6	1 140	29.4	453	11.7	73	1.9
November 1918	1 873	766	40.9	590	31.5	406	21.7	94	5.0	17	0.9
October 1919	2 162	969	44.8	678	31.4	401	18.6	102	4.7	12	0.5

TABLE 3—RELATION OF AGE TO THYROID CONDITION—NEW PUPILS—1917

	Age									
	10 - 12		12 - 14		14 - 16		16 - 18		18 - 20	
	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent
Normal	330	56.1	521	41.3	460	40.3	176	34.4	21	18.8
Slightly enlarged	394	41.7	680	53.9	578	50.7	235	51.9	44	60.3
Moderately enlarged	21	2.2	59	4.7	98	8.6	60	13.2	8	11.0
Markedly enlarged			1	0.1	4	0.3	9	0.4		

TABLE 4—RELATION OF AGE TO THYROID CONDITION—NEW PUPILS—1918

	Age									
	10 - 12		12 - 14		14 - 16		16 - 18		18 - 20	
	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent
Normal	491	64.2	295	50.0	214	52.7	39	41.5	9	52.9
Slightly enlarged	267	34.8	276	46.8	168	41.4	49	52.1	6	35.3
Moderately enlarged	8	1.0	19	3.2	24	5.9	6	6.4	2	11.8
Markedly enlarged	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

mately 95 per cent are included in the age group from 10 to 12. Details of the relation of age to the clinical condition of the thyroid are given in Tables 3, 4 and 5.

TABLE 5—RELATION OF AGE TO THYROID CONDITION—NEW PUPILS—1919

	Age									
	10 - 12		12 - 14		14 - 16		16 - 18		18 - 20	
	Num ber of Cases	Per Cent	Num ber of Cases	Per Cent	Num ber of Cases	Per Cent	Num ber of Cases	Per Cent	Num ber of Cases	Per Cent
Normal	743	76.7	419	61.8	199	49.6	53	51.9	7	58.3
Slightly enlarged	215	22.2	229	35.3	170	42.4	43	42.2	5	41.7
Moderately enlarged	11	1.1	20	2.9	31	7.8	6	5.9	0	0.0
Markedly enlarged	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0

TABLE 6—ANALYSIS OF RECORDS OF NEW PUPILS—NEGROES—1919

	Age					
	10 - 12		12 - 14		14 - 16	
	Number of Cases	Per Cent	Number of Cases	Per Cent	Number of Cases	Per Cent
Normal	5	59.0	7	53.9		
Slightly enlarged	4	40.0	5	38.5	3	75.0
Moderately enlarged	1	10.0	1	7.6	1	25.0

For reference and comparison the original survey of all pupils (April, 1917), is given in Table 3, while in Tables 4 and 5 are given the results of the surveys of new pupils for 1918 and 1919, respectively. It should be emphasized, that in the 1917 examination, 43.9 per cent of the girls in the 10-12 years age group had enlarged thyroids, that in the 1918 examination 35.8 per cent had enlarged thyroids, and that in the 1919 examination 23.2 per cent had thyroid enlargements. This is important from the standpoint of the age at which the prophylactic treatment should be started. When this work was begun, no data of this kind were available, and the fifth grade was arbitrarily chosen as the lower limit, because our limited facilities made it necessary to confine our efforts to what seemed to be the most important age periods. We have seen only forty instances of moderately enlarged glands and no instance of marked enlargement in the 10-12 years age group, and as very striking therapeutic effects are seen in these slight hyperplasias it makes little difference in the ultimate result. If, however, one had to depend entirely on prevention it would be necessary to begin at an earlier age.

There appears to be no noteworthy difference in the incidence of thyroid enlargements between white and colored children. The data are, however, insufficient for any definite conclusion. The data on the twenty-seven colored children are given in Table 6.

EFFECT OF PROPHYLACTIC TREATMENT

The prophylactic treatment as carried out for the past two years consists of the administration of 2 gm sodium iodid, given in 0.2 gm doses daily, for ten consecutive school days, repeated each spring and autumn. The general data of those pupils not taking the treatment are given in Table 7, and of those taking the treatment in Table 8. Only pupils with two or more consecutive examinations have been included in the tabulations. A considerable number of pupils, both taking and not taking the treatment, have been omitted because they missed one examination, although otherwise their records were complete. Two thousand, three hundred and five pupils are included in the tabulation.

TABLE 7—RECORD OF PUPILS NOT TAKING PROPHYLACTIC TREATMENT

Time Under Observation Mos	Normal				Slightly Enlarged						Moderately Enlarged					
	Unaltered		Increased		Unaltered		Increased		Decreased		Unaltered		Increased		Decreased	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
6	47	50.0	47	50.0	93	69.4	36	26.9	5	3.7	16	69.6	7	30.4	0	0.0
12	420	75.5	130	24.5	251	70.3	35	9.8	71	19.9	17	65.4	8	30.8	1	3.8
18	103	65.2	55	34.8	108	74.5	18	12.3	19	13.1	11	57.9	3	15.8	5	26.3
24	135	76.7	41	23.3	106	79.7	8	6.0	19	14.3	9	60.0	3	20.0	3	20.0
30	205	75.1	68	24.9	140	73.7	30	15.8	20	10.5	4	66.7	0	0.0	2	33.3

of those not taking treatment, and 2,190 in the tabulation of those taking treatment. Further, it was necessary to tabulate the results with reference to the length of time under observation. As the prophylactic treatment was given at intervals of six months, we have used this interval as the unit and grouped the pupils according to the periods under observation, 6, 12, 18, 24 and 30 months respectively. Only the results of three groups (normals, slightly enlarged, and moderately enlarged) are included because the fourth group (markedly enlarged) is too small. A comparison of the two tables brings out striking differences between those not taking and those taking iodine. These differences are manifested both in *prevention* of enlargement and in a *decrease* in the size of existing enlargements, i.e., therapeutic effect.

*Prevention*—This effect is shown in the columns marked “unchanged” and “increased.” Taking the totals for the five six month periods (Table 9) the following results were obtained. Of those that were normal at the first examination and did not take iodine, 347, or 27.6 per cent, have enlarged thyroids, while of those that were normal at the first examination and took iodine as outlined, two, or 0.2 per cent,

have enlarged thyroids These two instances of enlargement were investigated The first pupil, M T, age 16, had her thyroid examined and classified as normal May 2, 1917, Oct 17, 1918 and Dec 3, 1918 At the examination Oct 15, 1919, it was classified as slightly enlarged This girl had taken 2 gm of sodium iodid during each of the five possible periods, May, 1917, November, 1917, May, 1918, December, 1918 and May, 1919 A special examination was made Jan 13, 1920 The enlargement of the thyroid was verified The enlargement was acquired as opposed to congenital, as shown by the absence of a pyramidal process or thyroglossal tract The tonsils were markedly enlarged, nearly meeting in the midline when the mouth was widely opened

TABLE 8—RECORD OF PUPILS TAKING PROPHYLACTIC TREATMENT

Time Under Observation Mos	Normal				Slightly Enlarged						Moderately Enlarged					
	Unaltered		Increased		Unaltered		Increased		Decreased		Unaltered		Increased		Decreased	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
6	17	94.4	1	5.6	54	69.2	1	1.3	23	29.5	9	81.8	0	0.0	2	18.2
12	344	99.7	1	0.3	187	45.5	0	0.0	224	54.5	10	23.8	0	0.0	32	76.2
18	73	100.0	0	0.0	72	52.3	1	0.7	64	46.7	7	28.0	0	0.0	18	72.0
24	184	100.0	0	0.0	72	37.9	1	0.5	117	61.6	2	7.7	0	0.0	24	92.3
30	288	100.0	0	0.0	92	28.5	0	0.0	231	71.5	1	2.6	0	0.0	38	97.4

TABLE 9—SUMMARY—RECORDS OF PUPILS TAKING AND NOT TAKING PROPHYLACTIC TREATMENT

	Taking		Not Taking	
	Totals	Per Cent	Totals	Per Cent
Normal				
Unchanged	906	99.8	910	72.4
Increased	2	0.2	347	27.6
Slightly Enlarged				
Unchanged	477	41.9	698	72.8
Increased	3	0.3	127	13.3
Decreased	659	57.8	134	13.9
Moderately Enlarged				
Unchanged	29	20.3	57	64.0
Increased	0	0.0	21	23.6
Decreased	114	79.7	11	12.4
Total	2,190		2,305	

They were abnormally hyperemic, and on direct questioning the pupil stated she was subject to recurrent tonsillitis There was also slight enlargement of the lymphoid tissue at the base of the tongue and in the nasopharynx The general impression was that of a neurotic individual with general lymphoid hyperplasia

The second girl, aged 15, had her thyroid first examined and classified as normal Nov 27, 1918 At the examination Oct 16, 1919, it was classified as slightly enlarged This girl had taken 2 gm sodium iodid during each of the two available periods, November, 1918 and May, 1919 A special examination was made Jan 13, 1920, and the thyroid

enlargement was verified. Careful inspection revealed the presence of Hutchinson teeth, depressed nasal arch and interstitial keratitis. We considered the case one of neglected congenital syphilis.

Passing to Group 2, or those classified as having slightly enlarged thyroids at the first examination, it is seen among those not taking the prescribed treatment that 127, or 13.3 per cent, underwent further enlargement, while of those taking the prescribed treatment, three, or 0.3 per cent, underwent further enlargement. Two of these three pupils were again examined Jan 13, 1920. One, R. R., aged 14, was examined May 2, 1917, Oct 12, 1917 and Nov 26, 1918, and the thyroid classified as slightly enlarged, and at the examination Oct 16, 1919 the gland was classified as moderately enlarged. This girl had taken the prescribed treatment only during the last three available periods, May, 1918, November, 1918 and May, 1919. A special examination was made Jan 13, 1920 and the thyroid enlargement verified. In this case also the tonsils were enlarged and the seat of recurrent infections. The second case, V. S., aged 11, was examined Oct 22, 1917 and Nov 27, 1918 and the thyroid classified as slightly enlarged. At the third examination, Oct 16, 1919, it was classified as moderately enlarged and the special examination Jan 13, 1920, verified this finding. This girl had taken the prescribed treatment during the four available periods, November, 1917, May, 1918, December, 1918, and May, 1919. Superficial inspection failed to reveal the existence of any associated pathologic condition as was found in each of the first three cases mentioned. The fifth girl was not present for the special examination. These five cases are the only instances out of 2,190 pupils taking iodine that showed enlargement. For the group with slightly enlarged thyroids taking iodine, 447, or 41.9 per cent, remained unchanged, while of those not taking iodine, 698, or 72.8 per cent, remained unchanged.

Passing to the third group, or those classified as having moderately enlarged thyroids at the first examination, it is seen that of those taking iodine, twenty-nine, or 20.3 per cent, remained unchanged, while of those not taking iodine, fifty-seven, or 64.0 per cent, remained unchanged, of those taking iodine none increased, while of those not taking it, twenty-one, or 23.6 per cent, increased.

*Curative or Therapeutic Effect*—Although of secondary importance, the results are just as striking as those above described under prevention. These results are shown in the column marked "decreased." Of those pupils whose thyroids were classified as slightly enlarged at the first examination, and who took iodine, 659, or 57.8 per cent definitely decreased in size, while of those not taking the prescribed treatment, 134, or 13.9 per cent, decreased. Passing to the group

whose thyroids were classified as moderately enlarged at the first examination, 114, or 79.7 per cent, of those taking iodine showed definite decreases. In some the decrease in size was most striking and hardly to be believed had we not had actual measurements and descriptions of the condition previously. The reduction in several cases was as marked as one sees in the thyroid enlargement of young dogs, sheep or cattle following the use of iodine. It means that with similar anatomic conditions, i.e., uncomplicated hyperplasias of the thyroids, the degree of reaction is similar. Ordinarily, one does not obtain the striking therapeutic effect on human thyroid enlargements that is seen in animals. This, as pointed out in previous papers, is due, in large part, to the duration of the enlargement, the presence of adenomas, cysts, degenerations, hemorrhage, etc., which are common in all long standing human goiters, while very uncommon in the lower animals at the ages when these animals are usually observed. The therapeutic effect is a very



Fig 1—Moderate active hyperplasia, control specimen removed ten days after beginning administration of iodine (D—185a)

important supplement to prevention and makes it possible to begin prophylactic treatment in older pupils with the same practical result than would otherwise be possible.

#### DISCUSSION

Our observations on the prevention of simple goiter in man have extended over a period of thirty months. The disease is as easily prevented in man as in fish or in domestic animals.

Of 2,190 pupils taking 2 gm sodium iodide twice yearly, five have shown enlargement of the thyroid, while of 2,305 pupils not taking the prophylactic, 495 have shown enlargement of the thyroid. Of 1,182 pupils with thyroid enlargement at the first examination and who took the prophylactic, 773 thyroids have decreased in size, while of 1,048 pupils with thyroid enlargement at the first examination and who did not

take the prophylactic, 145 thyroids have decreased in size. These figures demonstrate in a striking manner both the preventive and the therapeutic effects. There is an error in the above figures in that many pupils listed as not taking iodine have taken iodine in one or another form outside the school jurisdiction. No attempt has been made to detect or estimate this error.

In the practical application of the preventive treatment, one must keep in mind the three periods when simple thyroid enlargements most commonly occur, viz., (1) fetal, (2) adolescence and (3) pregnancy.

(1) Prevention of goiter in mother and fetus is as simple as that occurring during adolescence. Practically, it would seem that it is a charge or responsibility of individual members of the medical profession supplemented with public education.

(2) The prevention of goiter of adolescence, on the other hand, should be a public health measure under state, county or municipal



Fig 2—Same gland as Figure 1, specimen removed forty-four days after beginning administration of iodine

control. The existing systems of organization of the schools, public and private, is sufficient to handle all the details without additional aid or expense. Education of the pupils would be combined with the actual administration so that after leaving school they could continue the treatment, if necessary. Physicians in industrial medicine could render an important service in this field. Thyroid enlargement is approximately six times as frequent in girls as in boys. It is a social economic question each community must decide whether it will include both sexes. Likewise, as to the age of beginning and stopping the use of iodine. In this climate probably the maximum of prevention, coupled with the minimum of effort, would be obtained by giving it between the ages of 11 and 17 years. As applied to our schools it would mean beginning with the fifth grade.

*Manner and Form of Administration* —As previously stated, iodine is taken up by the thyroid gland when given by mouth, by inhalation, or by external application. Weith<sup>2</sup> reports favorable therapeutic effects from inhalation of iodine as carried out by suspending a wide mouthed bottle containing a 10 per cent tincture of iodine in the school room. Waste and lack of control of amounts taken are the most obvious objections. Similar objections hold in case of external application. Some form of oral administration seems most practical and economical. The addition of iodine or a salt of iodine to the water supply as we have done in preventing goiter in fish might be considered. There are obvious objections to such a plan. It would entail enormous waste. It is applicable only when there are installations, i. e., in towns and cities, and depending on the chemical impurities in water interactions might throw out the iodine. The most feasible oral method would seem to be the individual administration of definite small amounts, either in solution or as tablets. The cheapest salt, sodium iodide, could be given in either form. Manufacturing pharmacists state that sodium iodide could be prepared very cheaply in tablet form protected from the action of water and light. For private use, the well known U S P preparations, syrup of ferrous iodide and syrup of hydriodic acid are excellent.

*Amounts of Iodine to be Used* —An ounce of syrup of ferrous iodide or hydriodic acid given over a period of from two to three weeks and repeated twice yearly would seem ample. As a public health measure, we have used 2 gm of sodium iodide given over a period of two weeks and repeated twice yearly. This dosage has prevented enlargement of the thyroid in more than 99 per cent of the children in this mildly goiterous district. It is our opinion that much smaller amounts would suffice for healthy children and healthy pregnant women, provided the period of taking was prolonged, i. e., 1 gm sodium iodide distributed over a month would accomplish as good thyroid effects as 2 gm given over a period of two weeks.

The prevention of thyroid enlargement in individuals with other diseases or residing in extremely goiterous districts, as in some glacial valleys of Alaska and British Columbia, certain districts in the Alps and Himalayas, might require larger amounts of iodine for normals than above indicated. Our data of the clinical condition of four of the five cases that enlarged during the administration of 2 gm of sodium iodide, twice yearly, suggest that in infections (chronic catarrhal or suppurative tuberculosis, syphilis, etc.) and possibly also in conditions like chlorosis, osteomalacia, lymphatism and exophthalmic goiter, such amounts might not control the thyroid growth. In such conditions there

<sup>2</sup> Weith    Goiter and Iodine in the School, Cor-Bibl schweiz Aerzte 49  
1474 1919



may be a greatly increased demand for the thyroid hormone or the organism's ability to store iodine in the thyroid may be impaired. There is a great deal of clinical evidence for the first view and none at present in support of the second.

*Effect of Iodin on the Thyroid Gland*—This is manifested in two ways (1) on the iodine store and (2) on the histologic condition. Both of these effects have been fully described in previous papers.<sup>3</sup>

*Effect on the Store* If the thyroid gland is not saturated with iodine (i. e., contains less than 4 mg per gm of dried gland) it is taken up readily by the cells following its administration in any form and in any manner thus far studied. An increase in the iodine content of thyroid may be demonstrated in a few seconds following the injection of a soluble salt into the circulation.<sup>4</sup> Iodine thus taken up is held by the cells until elaborated into the physiologically active hormone, when any

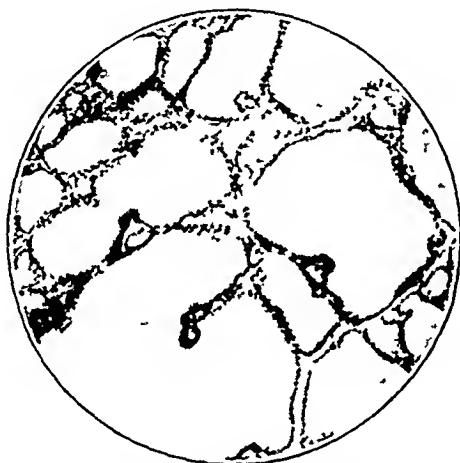


Fig 3—Same gland as Figures 1 and 2, specimen removed seventy-eight days after beginning administration of iodine. Total amount of iodine given, 90 mg.

excess is excreted into the follicular spaces and stored in the so-called colloid. Two factors then are concerned in the storage of iodine in the thyroid: (a) the capacity of the gland cells to take up and elaborate the

3 Marine, D. On the Occurrence and Physiological Nature of Glandular Hyperplasia of the Thyroid (Dog and Sheep) Together with Remarks on Important Clinical Human Problems, *Bull Johns Hopkins Hosp* **18** 359, 1907. Marine, D., and Lenhart, C. H. Colloid Glands (Goiters) Their Etiology and Physiological Significance, *Bull Johns Hopkins Hosp* **20** 131, 1909. Marine, D., and Lenhart, C. H. Effects of the Administration or the Withholding of Iodine-Containing Compounds in Normal, Colloid or Actively Hyperplastic Thyroids of Dogs, *Arch Int Med* **4** 253, 1909. Marine, D. Quantitative Studies on the in vivo Absorption of Iodine by Dogs' Thyroid Glands, *J Biol Chem* **22** 547, 1915.

4 Marine, D., and Rogoff, J. M. The Absorption of Potassium Iodide by the Thyroid Gland in vivo Following Its Intravenous Injections in Constant Amounts *J Pharm & Exper Therap* **8** 439, 1916.

hormone and (b) the capacity of the colloid material to store the product. It is evident, then, that to obtain maximum thyroid effects from a minimum amount of iodine, it should be administered in amounts not to exceed the capacity of the cells at any given time to handle it. As has been shown, the elaboration of the hormone proceeds slowly<sup>5</sup> in the most active thyroids. Also when one recalls that from 4 to 5 mg of iodine per gm of dried gland, or from 25 to 30 mg, is the total storage capacity of a normal thyroid, it is clear that small amounts of iodine (a few mg) given daily for a long period of time (a month or more) would produce optimum thyroid effects. In the school work, a compromise was found necessary, increased amounts and decreased time of administration.

**Effect on Histology of the Thyroid.** It has been shown that the minimum amount of iodine store necessary to maintain normal or quiescent thyroid structure is quite constant for mammals<sup>6</sup>. In the dog, sheep, human and pig thyroid it is approximately 1 mg per gm of dried gland, and immediately the percentage is reduced below the minimum, hypertrophic and hyperplastic changes begin and continue until the store of iodine has again been raised above the minimum requirements, when involution takes place. This cycle may be repeated many times in the same individual under natural or experimentally controlled conditions. In young dogs, with active hyperplasia, involution is usually complete in from fourteen to twenty-one days after beginning the administration of iodine. The histologic features of this involution have been described in detail in other papers, but for reference three microphotographs illustrating it are reproduced (Figs 1, 2 and 3).

**Untoward Effects.**—No obvious case of exophthalmic goiter has developed, although such cases have been carefully looked for. An occasional instance of iodine idiosyncrasy (iodism), amounting to less than 0.5 per cent of the cases, was noted. Most of the cases were very mild and the girls did not stop the treatment. As an untoward effect it is negligible.

#### SUMMARY

Observations on the prevention of simple goiter in man on a large scale have extended over a period of thirty months. The results show that it may be prevented very simply and cheaply in normal individuals. While thyroid enlargements of adolescence are more common, they are

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<sup>5</sup> Marine, D., and Rogoff, J. M. How Rapidly Does the Intact Thyroid Gland Elaborate Its Specific Iodine Containing Hormone? *J. Pharm. & Exper. Therap.* **9** 1, 1916.

<sup>6</sup> Marine, D., and Williams, W. W. Relation of Iodine to the Structure of the Thyroid Gland, *Arch. Int. Med.* **1** 349, 1908. Marine, D., and Lenhart, C. H. Further Observations on the Relation of Iodine to the Structure of the Thyroid Gland in the Sheep, Dog, Hog and Ox, *Arch. Int. Med.* **3** 66, 1909.

not more important than those occurring in mother and fetus. Prevention of adolescent goiter is properly a public health problem, while the prevention of fetal and maternal thyroid enlargements is largely a responsibility of individual physicians. The presence of pathologic conditions may modify the result of the prophylactic treatment in individual cases. While such instances are rare they are important and merit detailed reports.

# FURTHER OBSERVATIONS ON THE T WAVE OF THE ELECTROCARDIOGRAM OF THE DOG FOLLOWING THE LIGATION OF THE CORONARY ARTERIES \*

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In a former communication <sup>1</sup> it was stated that the T wave of the electrocardiogram of the dog was a marked negative phase on the day following the ligation of branches of the left coronary arteries. This wave remained negative for a period of three to five days and then gradually became positive. The work embodied in this report was undertaken to further these observations and, if possible, inquire into the cause of the negative T wave.

The anesthetic, artificial respiration and the method of exposing the heart were the same as employed in the former work. Electrocardiograms were taken daily of those dogs that survived the operation. On the second or third day following the operation they were anesthetized and the heart was again exposed. The movement of the heart was noted, especially that portion in which the blood supply had been disturbed.

## RESULTS OF LIGATION OF THE CORONARY ARTERIES

In twenty dogs various branches of the ramus descendens and of the circumflexus sinistra were ligated. Sixteen survived the operation. Fourteen of these, on the day following the operation, gave an electrocardiogram in which the T wave was markedly negative (Fig 1). In one of the exceptions the necropsy showed that the lumen of the ligated vessel had not been completely occluded. In the other case, collateral circulation had been established to a remarkable degree.

The negative phase of the T wave was greatest in those dogs in which the blood supply to the apex was most disturbed, as when two or more branches of the ramus descendens and circumflex sinistra, that supplies this area, were ligated. Individual differences seemed to vary with the amount of collateral circulation that was established.

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\* From the Medical Department of Rush Medical College and Presbyterian Hospital.

\* This investigation was aided by funds given by Mrs C H McCormick and Mr R T Crane, Jr.

1 Smith, Fred M. The Ligation of Coronary Arteries with Electrocardiograph Study, Arch Int Med 22 8 (July) 1918.

The striking features of the movement of the normal ventricles of the dog are a shortening of all the diameters and a tilting of the apex to the right during the systolic period. A satisfactory method of observing these movements was to place a superficial row of sutures at regularly spaced intervals on the longitudinal and transverse diameters in the form of a cross over the area chosen for observation. Those hearts in which branches of the left coronary artery had been ligated, showed a decrease in the activity of that portion in which the circula-

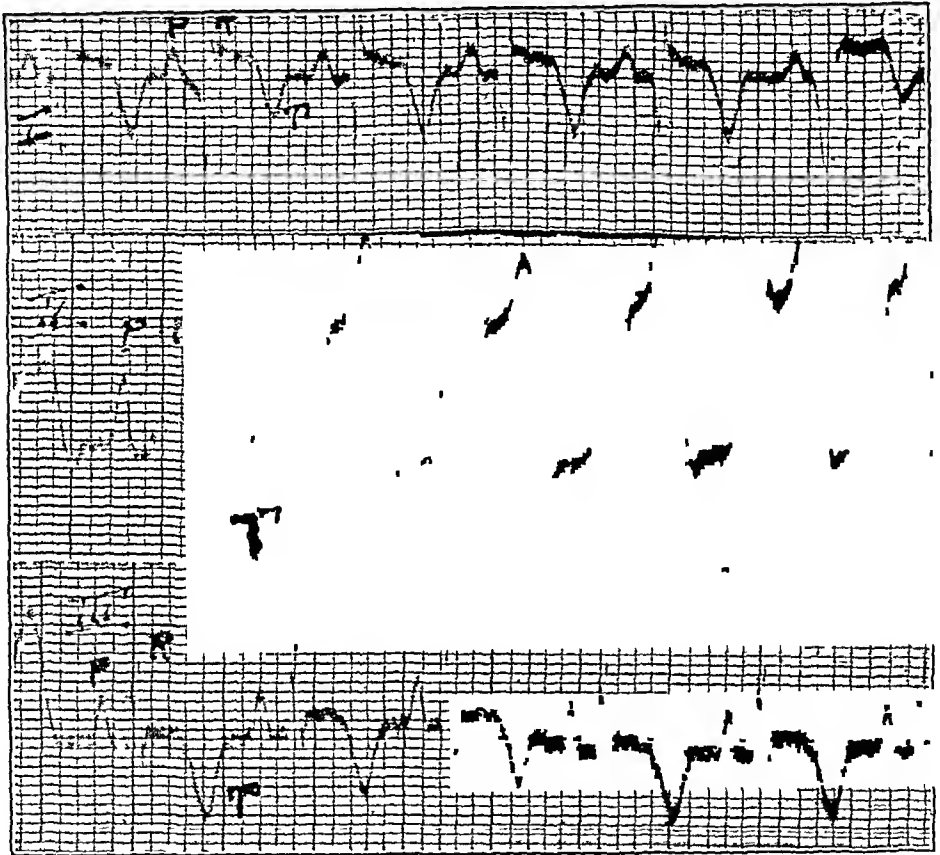


Fig 1—Leads I, II and III of a dog one day following ligation of branches of the left coronary arteries. The T wave is a negative phase.

tion had been disturbed. During the systolic period none of the diameters were shortened as in the normal contracting cardiac tissue. The degree of lessened activity and the extent of the area to which it was confined varied in individual cases with the size and number of vessels ligated and the amount of collateral circulation that was later established.

In eight dogs the right coronary artery was ligated. Three died the following night. In the remaining five a necropsy was performed on the second or third day after death. In no instance did the ligation of this artery appreciably affect the direction of the T wave.

# THE EFFECT OF COOLING AND HEATING VARIOUS AREAS OF THE VENTRICLES

In experiments on the normal heart of the dog, the effects on the T wave of the applications of heat and cold to various areas were observed. The heat was applied by means of small pledgets of cotton which had been soaked in water of 120 F temperature. Areas of the heart were cooled by the application of pledgets of cotton which had been soaked in ice water or by the application of a pencil of ice. More satisfactory results were obtained by the use of ethyl chlorid

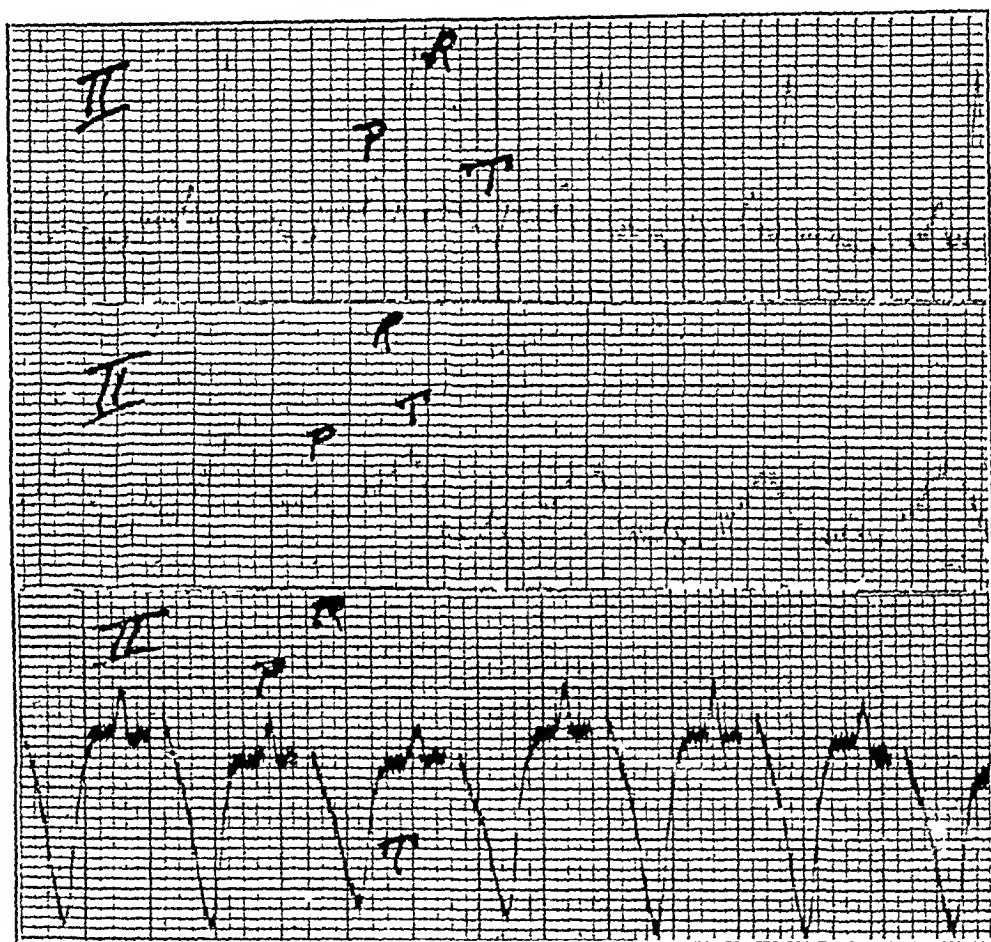


Fig 2—Lead II Top control

Middle Taken following the application of heat to the apex The T wave has changed to a positive phase

Bottom Taken following the application of ethyl chlorid to the apex The T wave is sharply negative

By means of this agent, the cooling could be more definitely localized on the desired areas of the heart and was employed in most of the experiments instead of the ice or ice water

The cooling of the apex by either of these agents produced a negative T wave similar in character to that following the ligation of the branches of the left coronary artery (Fig 2) When the middle

anterior surface of the left ventricle was cooled, this wave was much less negative and cold applications to the anterior basal surface had no effect. The cooling of various areas of the right ventricle did not change the electrocardiogram, except when applied to the basal region, in which case the height of the T wave was increased in some instances. The application of heat had the opposite effect to that of cold. The greatest change was produced when the heat was applied to the apex. The "T" became markedly positive. A negative condition of this wave, produced by cooling, could readily be changed to a positive by the application of heat. There was a decrease in the activity of that portion of the heart that was cooled. This was most marked when ethyl chlorid was used.

#### THE EFFECTS OF THE INJECTION OF BICHLORID OF MERCURY AND NITRIC ACID

The attempt was made to damage isolated areas of the myocardium by mercuric bichlorid (1 1,000) and nitric acid. These substances were injected into the region of the apex by means of a Luer syringe and a small hypodermic needle. The changes produced in the electrocardiogram by these agents were similar. The first effect was an increase in the height of the T wave. Later the R and T wave became fused into one. In one instance, following the injection of nitric acid, the R wave became smaller. Because of the difficulty of limiting the effects of these caustics to definite areas of the cardiac muscle this method was discontinued after four experiments.

#### COMMENT

Phonocardiograms show that the T wave appears just before the second cardiac tone. It, therefore, may be regarded as representing the end of the systolic period of the ventricles. The most generally accepted interpretation of this wave is that it is produced by the final activity of the base of the ventricles. This conception is based in the main on the views of the following investigators. Burden-Sanderson and Page,<sup>2</sup> in 1880 and 1883, studied the electrical reaction of the ventricles of the frog and tortoise by means of the capillary electrometer. They showed that when heat was applied to the muscle in the region of one pole, the excitation period in this area was shortened. In 1892, Bayliss and Starling<sup>3</sup> made similar observations on the heart of mammals. They concluded that the final ventricular variation was produced by a prolongation of the excitation at the base

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<sup>2</sup> Quoted from Mines<sup>1</sup>

<sup>3</sup> Bayliss and Starling. *Internat Monatschr f Anat u Physiol* 9 256

over that at the apex. Later Gotch<sup>4</sup> employed similar methods. He agreed with Bayliss and Starling that the T wave was produced by the final negativity at the base. He, however, concluded that this late condition at the base was due to the return of the excitation from the apex rather than a prolongation of the excitation at the base over that at the apex, as held by the two former investigators. Gotch worked on the supposition that the heart develops from the primitive cardiac tube in which the contraction wave travels from the venous to the arterial end. His conclusions were based on experiments in which he showed that the area in the vicinity of the aorta became electro-negative later than did other points on or away from the base of the ventricles.

Einthoven,<sup>5</sup> and also Krause and Nicolai,<sup>6</sup> agree with the former investigators that the final negativity at the base of the ventricles is responsible for the T wave. They also differ as to the manner in which this late negativity is produced. In this respect Einthoven seems inclined toward the conception of Bayliss and Starling, while Krause and Nicolai possibly agree more with the interpretation of Gotch.

Mines<sup>7</sup> has shown that the T wave of the frog can be changed to a marked positive phase by warming the apex. MacLeod<sup>8</sup> considers the production of a positive T wave in the frog from that which is normally slightly negative, by hurrying up the contracting process at the apex by heat, as convincing evidence in favor of the prevailing interpretation of the last ventricular phase of the electrocardiogram.

Samajloff,<sup>9</sup> and also Dale and Mines,<sup>10</sup> have studied the changes produced in the electrocardiogram of the frog by the stimulation of the sympathetic and vagus nerves. They state that stimulation of the sympathetic usually increases the height of the T wave, while stimulation of the vagus changes it to a sharp negative phase. Dale and Mines concluded that vagus stimulation caused the excitation to last relatively longer at the apex, while stimulation of the sympathetic increases the duration at the base.

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4 Gotch, F. The Succession of Events in the Contracting Ventricles as Shown by Electrometer Records (Tortoise and Rabbits), *Heart* **1** 235, 1909, also *Proc Roy Soc* **79** B, p 273.

5 Einthoven. *Arch Internat de Physiol* **4** 132, 1906, *Arch f d Ges Physiol* **122** 517, 1908.

6 Krause and Nicolai. *Das Elektrokardiogram des Gesunden und Kranken Menschen*, Leipzig, 1910.

7 Mines, G. R. On Functional Analysis by the Action of Electrolytes, *J Physiol* **46** 188, 1913.

8 Macleod. *Physiology and Biochemistry*, C. V. Mosby & Co., 1918.

9 Samajloff. Quoted from Dale and Mines<sup>10</sup>.

10 Dale, Dorothy and Mines, G. R. The Influence of Nerve Stimulation on the Electrocardiogram, *J Physiol* **46** 319, 1913.



Hoffmann,<sup>11</sup> and Eyster and Meek,<sup>12</sup> differ somewhat from the opinions that have hitherto been expressed. They interpret the electrocardiogram as being the expression of two processes occurring in the heart muscle, the excitation and the contraction of the muscle. They consider the R wave to be the manifestation of the passage of the stimulus over the bundle of His and its ramifications to the papillary muscles and the T wave, the resultant of the contraction of the ventricles. Even though they differ in this respect, Eyster and Meek state that one of the important factors in determining the size and direction of the T wave is the relative degree of contraction in the base and apical regions of the ventricles.

On the basis of the prevailing conception of the cause of the T wave the most plausible explanation of our results is that the negative phase was produced by the prolongation of the excitation at the damaged apex over that of the basal portion of ventricles. The marked negative T wave on the day following the ligation of branches of the left coronary artery, especially those that supply the apex, is presumably explained on the same grounds, as the negative phase following the cooling of the apex. In the latter instance this change in the T wave subsided soon after the cooling agent was withdrawn. In the former, however, it lasted from three to five days. After this time a certain degree of collateral circulation becomes established, fibrous tissue cells begin to appear in the area of disturbed circulation, and those factors that delay the excitation no longer exist. In our experiments the size and direction assumed by the T wave were most influenced by altering the condition of the apex. This can be better understood by assuming the apex to be the lower pole of the heart. On this basis, the T wave should be influenced in the opposite manner by adopting similar measures at the base of the ventricles. In conformity to this notion there was some increase in the size of the T wave when the base of the right ventricle was frozen with ethyl chlorid in some of the experiments. These results agree with those obtained by Eppinger and Rothberger<sup>13</sup> who employed similar methods. The fact that those measures which produced striking effects on the T wave when applied to the apex do not have the proportional opposite effect when applied to the base may be due to a more definite localization of the lower pole at the apex than the upper pole at the base.

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11 Hoffmann. Quoted from Eyster and Meek<sup>12</sup>

12 Eyster, J. A. E., and Meek, W. J. The Interpretation of the Normal Electrocardiogram, a Critical and Experimental Study, *Arch. Int. Med.* **11** 204 (Feb.) 1913.

13 Eppinger and Rothberger. Quoted from Eyster and Meek<sup>12</sup>

## CONCLUSIONS

1 In twenty dogs two or more branches of the ramus descendens and circumflex sinistra were ligated. Sixteen survived the operation. Fourteen of these gave an electrocardiogram on the following day in which the T wave was a sharp negative phase. The two exceptions were explained at the necropsy. The size that the T wave assumed in the opposite direction varied with the amount of disturbed circulation at the apex.

2 In eight dogs the right coronary artery was ligated. In five of these electrocardiograph studies were made on the day following the operation. The T wave was not appreciably affected by the ligation of this artery.

3 The application of cold had the most marked effect when applied to the apex. A negative phase always resulted. When the middle anterior surface of the left ventricle was cooled the T wave was less negative, and cold applications to the anterior basal surface produced no change. The cooling of various areas of the right ventricle did not affect the T wave, except when applied to the basal region, in which case the height was increased in some instances. When heat was applied the opposite results were obtained.

4 The direction that the T wave assumed in these experiments can best be explained on the prevailing conception that it is produced by the final activity of the base, and that the measures adopted either prolonged or delayed the activity at the apex.

It is a great pleasure to acknowledge my indebtedness to Dr. James B. Herrick for his suggestions.

# SEQUENCE AND ARRANGEMENT OF PALLOR AND REDNESS IN IRRITATED SKIN OF NORMAL AND DERMOGRAPHIC INDIVIDUALS

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The interesting succession of colors which characterizes dermographism has been studied by Jankowsy, Lapinsky and others. It is well known that the lesions not only undergo alternations of pallor and redness, but that two or more zones of alternating pallor and redness may be observed simultaneously. A case of Raynaud's disease, presenting similar zones and undergoing similar alternations of color, suggested that these changes might be of fundamental importance and widespread occurrence. The following series of experiments was accordingly planned, with a view to ascertaining whether the zones of pallor and redness, or the occurrence of pallor followed by redness, were also characteristic of lesions produced by various other irritants.

The irritants used were mechanical, thermal, chemical and electric. Mechanical irritation or injury was provoked by stroking the skin with a blunt object, such as a toothpick, by scratching the skin with a needle, and by pinching a bit of skin between the jaws of a hemostat. Thermal injury was provoked by applying a hot iron or a heated glass rod to the skin. Mosquito bites afforded the opportunity to observe the effects of chemical irritants, and the electrolytic needle with galvanic current constituted the injurious electrical agent. Finally, carbon dioxid snow was applied for producing lesions due to lowered temperature.

The toothpick was applied to the skin of three dermographic and two hundred normal persons. The needle scratch was applied to eighteen individuals. The carbon dioxid snow was applied to the skin of two normal persons and one person suffering from Raynaud's disease. The electrolytic needle was applied to one dermographic person and to three normal persons. One person who was burned accidentally afforded opportunity to record the stages of a burn, three persons who were bitten by mosquitoes furnished the basis of observations on poisoned wounds. Finally, an experimental animal (dog) was subjected to all the varieties of injury just mentioned and to one other, namely, pinching or crushing with a hemostat.

There was a striking similarity between the lesions produced by the various means enumerated, in that they all tended toward wheal formation. Virtually all lesions showed pallor over the contact spot immediately after the injury, and the pale spot usually became sur-

rounded by a peripheral red zone within a few minutes. Within from two to thirty minutes, the pale contact spot became pink, and in some instances the peripheral red zone also underwent a reversion of color, becoming pale.

The development of edema usually proceeded at a rate which produced visible elevation by the end of a few minutes, and this swelling was, in certain instances, associated with a secondary pallor at the contact spot. This was particularly true of dermographic lesions and lesions produced on normal skin by the application of carbon dioxide snow.

The carbon dioxide snow was applied in the form of a truncate crayon 2 cm in diameter. The lesions produced by this agent were typical wheals, but showed as many as four color zones at certain moments.

It is well known, that the wheal is the lesion characteristic of dermographism, and that formation of wheals constitutes the usual reaction of normal skin toward insect bites. This series of experiments tends to show that dermographic skin reacts like normal skin, and that both normal and dermographic skin react similarly toward mechanical and other forms of trauma.

Chambard and certain other authors have reported failure in the attempt to provoke dermographic lesions by electrical, chemical and thermal stimuli. A careful analysis of the dermographic lesion will show, however, that even the mechanical means must be applied in a certain manner before the formation of wheals is achieved. For instance, a flat-pointed tooth-pick one-eighth inch wide, drawn with moderate friction across dermographic skin, will cause an edematous streak along each edge of the path described, but the intermediate space does not become elevated until after the two margins coalesce in the center. Moreover, the cuticle of dermographic skin can be removed with "00" sandpaper without causing a wheal. These facts indicate that in dermographism the wheal is the result of mechanical forces acting according to a certain arrangement, extending over a certain area, and reaching a certain depth.

The fact that electrical, chemical and thermal stimuli have been applied to dermographic skin by some investigators without provoking wheals, can be explained on the ground that the extent and depth of tissue affected by the stimuli was probably dissimilar to that affected by the usual friction stroke, while, on the other hand, the occurrence of urticarial wheals as a result of soluble poisons circulating in the blood, lowered temperature, affecting the entire body surface, instrumentation of the urethra, and even intense emotion, appears to establish the hypothesis that there is an inherent tendency in the skin to react in one stereotyped fashion to all forms of irritant.

## CONCLUSIONS

1 The reactions observed in dermographism seem to be entirely analogous to those observed in normal skin, differing only in degree

2 All the irritants investigated (scratch, pinch, burn, electrolysis, freezing, mosquito bite, dermographic scratch) tend to cause (a) Initial pallor, (b) peripheral red zone, (c) reversion of color from pale to red, the latter commencing at the periphery and proceeding toward the center

3 The tissues studied tend to react in one stereotyped manner to all the irritants investigated

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# THE DETERMINATION OF VENTRICULAR PREDOMINANCE FROM THE ELECTROCARDIOGRAM

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Two recent articles containing much speculation and few facts have directed my attention to the necessity for a review of the subject of the electrocardiographic diagnosis of hypertrophy of one or the other ventricle of the heart. The original observations on this subject were that cases in which hypertrophy of the left ventricle might be expected showed a relatively tall R wave in Lead 1, with absence of an S wave in this lead, while Lead 3 shows a relatively small or absent R wave and a deep S wave. In like manner, cases in which hypertrophy of the right ventricle might be expected showed a relatively small R wave in Lead 1 and a deep S, while the S wave was absent in Lead 3 and the R wave relatively tall<sup>1</sup>. Einthoven demonstrated the fact that if the actual values of the largest waves of the Q R S group in Leads 1 and 3 were added together, the result would be equal to the value of the largest wave of this group in Lead 2. There is some slight error in this addition owing to the fact that the peaks of the waves do not occur at the same instant of the heart cycle in all three leads. He showed that throughout the Q R S group and in fact throughout the whole electrocardiogram if we consider the parts of the curve in the three leads which occur at the same instant of time then the value in Lead 1 + value in Lead 3 = value in Lead 2<sup>2</sup>. From the relative size and direction of these values in the three leads there can be calculated the direction of flow of current within the heart at that instant.

It soon developed that it was not the actual hypertrophy of one or the other ventricle which caused the changes in the electrocardiogram, but the relation of the state of hypertrophy of each ventricle to the other. If a heart had mitral stenosis and had also to oppose an increased blood pressure, then both ventricles would become hypertrophied and the electrocardiogram might show a normal relation of the height of the R waves in the three leads. Neither ventricle in this case would be predominantly hypertrophied, and for this reason it has become necessary to speak of the records as showing right or left ventricular predominance instead of hypertrophy.

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1 Einthoven, W. Le Telecardiogramme, Arch Internat de Physiol 4 132, 1906

2 Einthoven, W. Weiteres u d Elektrokardiogram, Arch f d ges Physiol 122 576, 1908

Various methods have been suggested for deriving from the electrocardiogram a mathematical expression of this relative predominance of one or the other ventricle. Einthoven considered that the current at the instant of the highest peak of the Q R S group would give such an index, and calculated from the size and direction of these peaks in the three leads the direction of the current within the heart which had caused these high peaks. This calculation was made by quite sound mathematics, and a table was published by him,<sup>3</sup> by the use of which it was very easy to determine the direction of the current within the heart which had produced corresponding waves in the three leads. This is simple enough when the peaks of the waves occur at the same instant of the heart cycle in all three leads, for then the formula  $\text{Lead 1} + \text{Lead 3} = \text{Lead 2}$  will be exactly fulfilled. When they do not occur at the same instant they are spoken of as being "out of phase," but even in such records it is usually possible to determine by inspection which parts of the Q R S groups of the other two leads correspond in time with the high peak of the lead showing the largest deflection. This is aided by bearing in mind that in right predominance it is usual to have the peaks of the R waves in Leads 2 and 3 practically simultaneous while the corresponding instant in Lead 1 will lie somewhere on the downward stroke between the peaks of R and S. Likewise, in left predominance records the peaks of R are practically in phase in Leads 1 and 2, and this instant will fall in Lead 3 at a point on the downward stroke between the R and S peaks. Rarely, however, a record will defy even this attempt at analysis.

Having determined the direction of the current which produced the largest deflection, Einthoven considered that those hearts which showed this angle within the sector between 40 and 90 degrees below a line drawn horizontally to the patient's left were hearts which showed a normal balance of the ventricular elements. Those which gave an angle above 40 degrees showed left predominance, while those which gave an angle which was to the patient's right of 90 degrees showed right predominance. This was in general agreement with the previous idea as to the relation of the R and S waves in Leads 1 and 3 to ventricular predominance, for the S waves become more prominent than the R, in Lead 1 at 30 degrees and in Lead 3 at 90 degrees.

Lewis suggested a method of obtaining an index of predominance by adding the value of  $R_1 - R_3$  to the value of  $S_3 - S_1$ .<sup>4</sup> He probably did this, although he did not attempt a theoretical explanation of this formula, from a belief that as  $R_1$  and  $S_3$  vary together, the first grow-

<sup>3</sup> Einthoven, Fahr and de Waart. Ueber die Richtung und die Manifeste Grösse der Potentialschwankungen, etc., *Arch f d ges Physiol* **150** 275, 1913.

<sup>4</sup> Lewis, T. Observations on Ventricular Hypertrophy, etc., *Heart* **5** 367, 1914.

ing smaller and the latter larger with increasing left predominance they must be governed by the left ventricle, and for a similar reason S1 and R3 must be governed by the right ventricle

White has suggested that  $(U1 + D3) - (D1 + U3)$  considering that U, the upper deflection and D, the largest of the downward deflections, whether it be a Q or an S, would represent opposing ventricles<sup>5</sup> His figure will, of course, only differ from Lewis' figure when Q is larger than S, so that it becomes the largest downward deflection

Carter has suggested that the sum of the downward deflections of each lead be subtracted from the upward, and that the resulting figures for the three leads be used to determine the direction of the current within the heart<sup>6</sup> When the resulting figures for the three leads cannot be made to agree with Einthoven's rule of  $\text{Lead 1} + \text{Lead 3} = \text{Lead 2}$ , by a little judicious scaling of the figures, he then recommends that the Lead 1 and Lead 3 values be used to determine the direction of the current, totally disregarding Lead 2

COMPARISON OF L/R WEIGHT RATIOS AND ELECTROCARDIOGRAPHIC PREDOMINANCE AS DETERMINED BY FOUR METHODS

Case	L/R Weight Ratio	Angle as Found by Einthoven's Method	Angle as Found by Carter's Method	Lewis' Formula	White's "Index"	Value Largest Wave of QRS Group	Lewis' Formula Reduced to R 10
I	2.63*	-10	-30	29.5	29.5	16.5	17.9
II	2.60	-70	-60	19.0	19.0	15.0	12.6
III	2.55*	-74	-75	17.5	16.5	15.0	11.7
IV	2.04	14	16	19.0	19.0	12.5	15.2
V	1.97*	79	75	-10.0	-8.0	13.0	-7.7
VI	1.94	45	30	8.0	8.0	11.0	7.3
VII	1.87	0	10	12.5	12.5	10.0	12.5
VIII	1.82	18	35	4.5	4.5	6.0	7.5
IX	1.60	82	115	-7.0	-7.0	6.0	-11.6
X	1.55*	4	-30	9.0	9.0	7.0	12.9
XI	1.38	78	90	1.5	1.5	6.5	2.3
XII	1.30*	79	95	-3.5	-5.0	5.0	-7.0
XIII	0.82*	101	150	-6.0	-6.0	6.0	-5.8
XIV	0.82	105	128	-15.5	-15.5	11.0	-14.1
XV	0.41	131	160	-77.0	-76.0	44.0	-17.5

\* The cases marked with asterisk are from Cotton's series, the remainder are from Lewis'

A great deal could be said about the theoretical merits of these different methods of estimating ventricular predominance. It can all be discarded, however, in the face of direct evidence such as we are able to obtain from two series of observations. One series of nine cases by Lewis<sup>4</sup> and one of six cases by Cotton,<sup>7</sup> have been reported in which the electrocardiogram and the actual weights of the ventricles

<sup>5</sup> White, P. D., and Bock, A. V. Electrocardiographic Evidence of Abnormal Ventricular Preponderance, etc., *Am J M Sc* **156**:17, 1918

<sup>6</sup> Carter, E. P. The Electrocardiogram and Ventricular Predominance, *Arch Int Med* **24** 638 (Dec.) 1919, also Carter, Richter and Greene *Bull Johns Hopkins Hosp* **30**:162, 1919

<sup>7</sup> Cotton, T. Observations on Hypertrophy, *Heart*, **6** 217, 1917

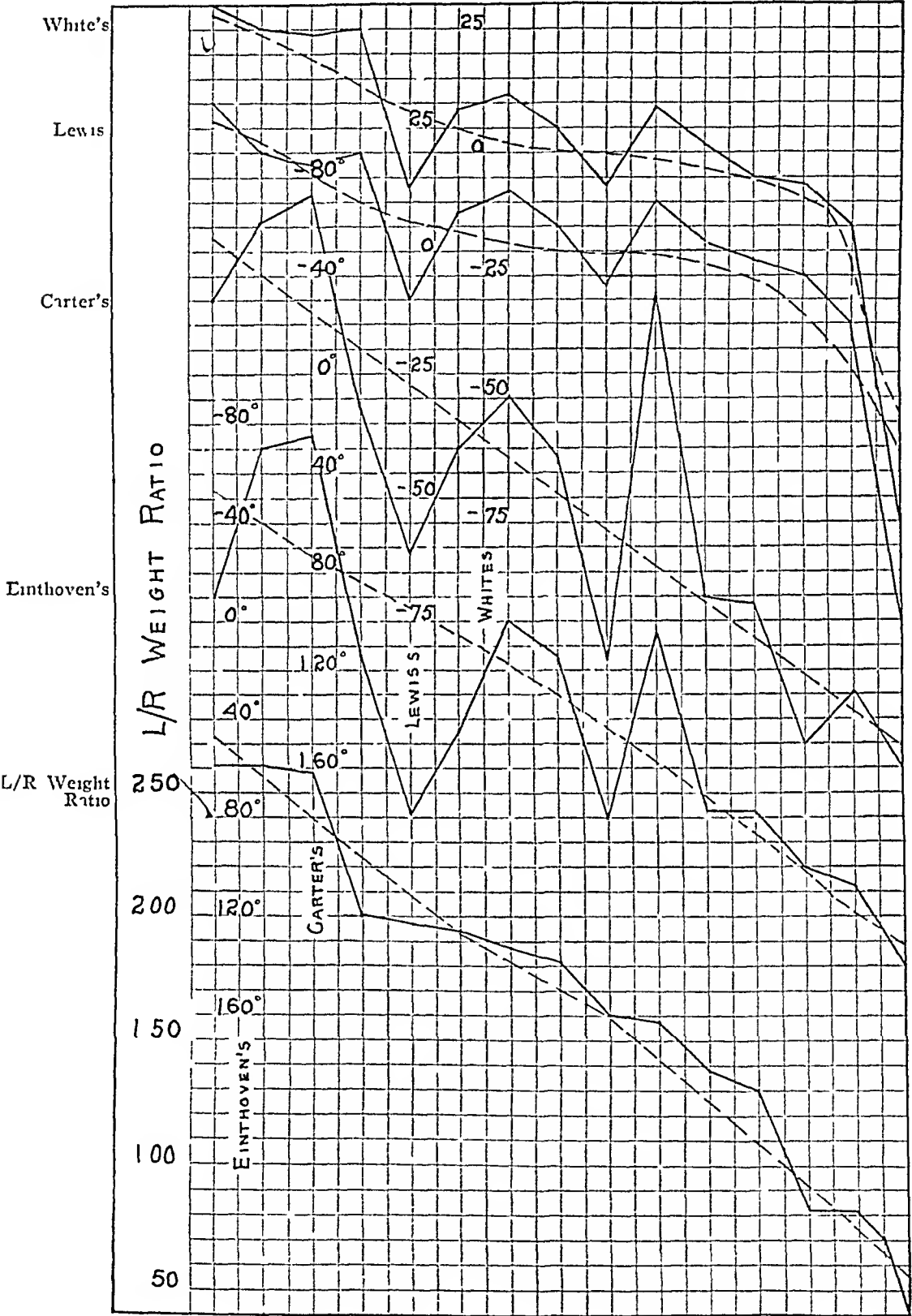


were obtained in the same patients. These fifteen cases have been arranged in the accompanying table according to the ratio of the ventricular weights as determined by Lewis and Cotton. From the published measurements of the Q R and S waves in the three leads, the electrocardiographic "predominance" has been calculated by the four methods which have been mentioned. The first column is the value of L/R obtained from the ventricular weights. The figures for the angle of the largest current as obtained by Einthoven's method are shown in the second column, the angle as obtained by Carter's method is in the third column, the figures by Lewis formula are in the fourth column, and White's "index" occupies the fifth column.

It is evident that all of these formulas give figures which follow in a general way the actual relation of the ventricular weights, but it is also evident that none of them enables us to place the heart very accurately in the scale of left or right predominance as actually determined by the weight relation. The normal variations of the L/R weight ratio have been determined in two series of thirty-four normal persons, whose ventricles were separated and weighed by Lewis<sup>4</sup> and by Cotton.<sup>7</sup> The average L/R ratio was approximately 1.80, the extreme variations being 2.17 and 1.47, the former probably representing a moderate left predominance and the latter a moderate right predominance. Three of the cases of the table have an L/R ratio larger than 2.17, and therefore may be considered to show definite left predominance, while five have a ratio less than 1.47 and show, therefore, a definite right predominance.

Figure 1 is a series of curves constructed from the table by using the values in the first five columns to obtain the height from the base line and the order of the cases from 1 to 15, as determined by their L/R weight ratio, to obtain the distance from the left hand ordinate. The weight ratio forms a smooth steadily declining curve, while all of the other curves, though in general declining, have many departures from smoothness. Individual cases vary considerably from the position in these irregular curves which they would be expected to occupy considering their L/R ratio. The dotted line drawn through each curve indicates the average course of this curve, and along this line our cases should lie. It is evident that the variations from this average obtained by the Lewis or the White formulas are less than the variations obtained by the other formulas, and, moreover, only three persons who had a normal weight ratio would be classed as having predominance by these methods while either of the other methods would have thus misplaced four cases.

In considering the basis of the Lewis and White formulas, it is evident that the size of the largest wave in the Q R S group, R or S,



CASE I II III IV V VI VII VIII IX X XI XII XIII XIV XV

Fig 1—Series of curves constructed from the table by using the values in the first five columns to obtain the height from the base line

as the case may be, will be an important factor in the resulting figure. The values for the largest waves in the electrocardiogram of each individual are shown in the sixth column of the table, and it is very interesting to note that they are larger in the right and left predominance cases than they are in those showing a normal balance. This is a wholly unexpected finding, and will well warrant a further study which is at present in progress. Considering this varying value of the largest waves, and the fact that the Lewis and White formulas are so evidently dependent on this value, it is not surprising that the curve of these cases obtained by these formulas show at first a steep descent as the diminishing degrees of left predominance are recorded, a more or less level stretch and then another steep descent as the increasing right predominance is met with. This fact made it seem advisable to correct the Lewis formula for the value of the largest wave in the record of the individual changing the Lewis figure, so that it would be proportional to a value of 10 mm for the largest wave. This formula would be "Lewis' figure  $X = R \div 10$ ". The figures obtained thus form the last column of the table. The variations in a curve constructed from these figures would be very great, so that this correction for the size of the largest wave offers no advantage.

Other formulas were tried attempting always to find a method of treatment of the electrocardiogram of these cases which would place the individual case near to the average position in the series which might be expected from the L/R ratio. They were all unsuccessful, none being any better than Lewis' formula which has such a desirable simplicity. The following were tried, but it seems unnecessary to publish the figures in view of their negative value.

1  $Q_1 + R_1 + S_3 - Q_3 - R_3 - S_1$ , a formula suggested by Lewis' recent analysis of the electrocardiogram.<sup>8</sup>

2  $Q_1 + S_3 - Q_3 - S_1$  was tried because the R wave has probably a factor from both ventricles, while Q and S have not.<sup>8</sup>

3  $R_1 + S_3 - S_1 - R_3 + \text{value of largest wave}$  another attempt to correct for the varying value of the R wave which has been noted with predominance of either ventricle.

4  $\frac{Q_1 + R_1 + S_3}{Q_3 + R_3 + S_1}$  an attempt to obtain an L/R ratio from the waves of the electrocardiogram which, according to Lewis,<sup>8</sup> depend on the respective ventricles.

5 The figure obtained by this last method was divided by the value of the largest wave.

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<sup>8</sup> Lewis, T. The Spread of the Excitatory Process in the Vertebrate Heart, Phil Tr Roy Soc London 207 221, Series B, 1916.

## DISCUSSION

As has been said, none of these methods attained the desired result of a uniformly varying series of figures, such as is given by the L/R weight ratio

Let us consider possible reasons why this object could not be achieved (1) It cannot be considered that the QRS group is not governed by the ventricular weight ratio for *all* of the formulas derived from the records give figures which agree in a general way in their placing of these cases in the series of predominance (2) It is possible that the cutting and weighing of the hearts might have been inaccurate so that the L/R ratio obtained does not express the proper position of the heart in the predominant scale This cannot be considered, for it would not cause more than relatively slight variations in the L/R ratio for relatively large errors in cutting, and so would not account for more than a very slight displacement of the heart from the position in the scale of predominance (3) There may have been errors in taking the electrocardiogram, but this cannot be considered at all likely in the hands of technicians who are familiar with the instrument as these men were (4) It is possible that the individual hearts varied in some other way than in their ventricular mass so as to change the electrocardiographic record from what it would otherwise have been, thus displacing it in the scale of predominance (a) The possibility that any of the cases of this series were suffering from blocking of one bundle branch may be discarded, for both of the workers are thoroughly familiar with the effect of this lesion on the record, and with the lack of relation between such curves as it would produce and the problem of ventricular predominance which they were investigating They would have discarded such cases (b) The anatomical position of the heart within the chest might vary sufficiently to be responsible for these electrocardiographic variations The respiratory movements of the diaphragm may cause a variation of as much as 30 degrees in the electrical axis of the heart,<sup>3</sup> and as it is a matter of common knowledge that in some types of individuals the heart may be more or less transversely placed on a high diaphragm as with full expiration, or in others may be more or less vertically placed with a low diaphragm as in full inspiration The transverse type of heart, if otherwise normal, gives an electrocardiogram approaching the left predominance type, while that of the vertical heart approaches the right predominance type, and it is suggested that it is probably such differences in position as this which are responsible for the electrocardiographic variations which have caused the normal cases of this series to appear to have a ventricular predominance By a similar mechanism a heart with a slight left predominance might give an electrocardiogram within the normal

limits of variation if it were vertically placed, or a slight right predominance might give a normal record if the heart were horizontal. The same mechanism would give to the electrocardiogram a form characteristic of a greater degree of predominance than the heart muscle actually shows if the left predominance case should lie transversely and the right predominance vertically. (c) Still another possibility has been suggested,<sup>9</sup> for the discrepancies existing between the ventricular weight ratio and the electrocardiographic "predominance." The size of the ventricular cavity may vary for the same weight of muscle. This may be expressed as dilatation. A small thick-walled ventricle may weigh the same as a large thin-walled ventricle. The different distribution of the electrical potential which this would cause

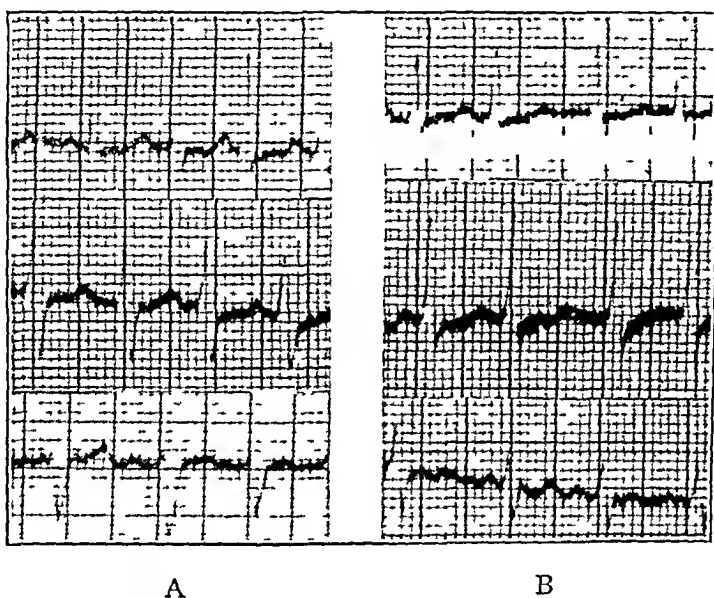


Fig 2—Two electrocardiograms taken from the same person, A, in the relaxed sitting position, B, in the erect sitting position

would in all probability have its effect on the electrocardiogram, and might well lead to such variations as were observed in this series. This point of view has been elaborately discussed quite recently by Fahr,<sup>10</sup> and certainly should command attention from anyone who considers this problem. It is a most difficult hypothesis to investigate, however, as it necessitates careful measurement of ventricular diameters as well as of ventricular weight.

Either of these latter suppositions would explain why the electrocardiograms of this series which vary from their expected position in the predominance scale, vary in the same direction, i. e., toward right or

<sup>9</sup> Personal communication from Dr. Hubert V. Mann.

<sup>10</sup> Fahr, G. An Analysis of the Spread of the Excitation Wave, etc., *Arch Int Med* 25:146 (Feb.) 1920.

toward left predominance, by whatever method the electrocardiogram is analyzed. The electrocardiogram has been caused to vary from the form which it would derive from the ventricular weight ratio by an unusually transverse or vertical position of the heart, or by what virtually amounts to a deformity of the heart, a dilatation of one chamber. It is impossible to decide between these hypotheses on theoretical grounds, but I must say that the former appears to be the more attractive theory.

Figure 2 shows two electrocardiograms taken one after the other from the same individual. Both were taken while he was sitting upright in a chair, but the one to the left, A, was taken with the erector spinae relaxed, the back bowed forward and the thorax fallen downward upon the abdomen so that the diaphragm was pushed up within it, the typical relaxed sitting position. The other record, B, was taken while he was sitting with the back straight and the chest forward in a normal, erect, sitting position. The electrical axis of record A is 6 degrees, while that of B is 46 degrees, the change by the Lewis formula is from 12 to 7, a change in this case due entirely to a change in the position of the diaphragm from high to normal. This patient was examined with the fluoroscope, and the anatomic axis of the ventricles roughly estimated in each position. This axis was found to rotate about 30 degrees. The degree of variation in the electrocardiogram which may result from a different position of the diaphragm is evident from this experiment, and also the fact that the anatomic axis varies at the same time in a similar manner.

#### CONCLUSIONS

The conclusions which may be drawn from these considerations are

- 1 That the form of the QRS group of the electrocardiogram is dependent in otherwise normal hearts on the relative weights of the two ventricles. An increase in the L/R ratio, such as would result from the left ventricle becoming relatively heavier, is accompanied by characteristic changes in the electrocardiogram, while if the L/R ratio is decreased, as by the right ventricle becoming relatively heavier, there are other equally characteristic changes in the record. These changes are the ones which have always been associated with the predominances, a tendency for  $R_s$  to be relatively small, and  $R_1$  and  $S_3$  to be relatively large in left predominance, while  $R_1$  is small and  $S_1$  and  $R_3$  are relatively large in right predominance.

- 2 Attempts to devise a formula from the QRS waves by which the heart can be placed properly in a series of ventricular predominance are successful only in a general way. Individual electrocardio-

grams vary greatly from the position in the scale of ventricular predominance which the ventricular weights alone would lead us to expect them to occupy

3 Of all the formulas which have been considered for determining the ventricular predominance from the electrocardiogram, the simplest to apply, the one giving the smallest apparent error in this series of fifteen cases, and the fewest variations of individual hearts from the position in the predominance scale which would be expected from the L/R weight ratio, is the formula suggested by Lewis of  $(R1 + S3) - (S1 + R3)$

4 It is suggested that the cause of these variations may well be that the hearts which varied from their expected position in the scale of predominance were of the markedly transverse or vertical type so that the electrocardiogram was distorted by this position of the heart

5 The suggestion as to ventricular dilatation causing these variations is also worthy of consideration

The diagnosis of ventricular predominance is far from being the most important information which the electrocardiogram gives us, but it is nevertheless very suggestive and important in certain cases. It is well, therefore, that we should realize that our conclusions as to predominance are not always in agreement with the ventricular weights, and that we earnestly try to find what are the factors which interfere with this agreement. The present suggestion as to the cause of the inexactness of the electrocardiogram seems to me to be quite reasonable, but reasonableness alone, without an experimental basis, should never be the foundation of any medical diagnostic procedure. It is hoped that this discussion will stimulate many observers to note the anatomic position of the heart in relation to the electrocardiographic "predominance" which is shown, and that as many as possible will combine with these factors the necropsy data, consisting of the actual relation of the ventricular weights, using Lewis' technic for cutting and weighing the ventricles<sup>4</sup> so that the results may be comparable with his, and also proper measurements of the ventricular size. Only in this way can the subject be eventually placed on a firm foundation

# THE EFFECT OF ACUTE YELLOW ATROPHY ON METABOLISM AND ON THE COMPOSITION OF THE LIVER\*

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In the present paper we report chemical analyses of the blood and urine made in a case of acute yellow atrophy for three days before death, together with analysis of the liver removed at necropsy three hours after death. The study was directed especially toward the nitrogen metabolism and the acid-base balance of the patient. Besides other determinations, including those of urea, quantitative estimations of the amino-acid nitrogen in the urine, blood and liver were performed for the first time in such a case, so far as we can ascertain.

The results are of interest in two connections: (1) the pathologic metabolism of acute yellow atrophy, and (2) the rôle of the liver in the normal handling of nitrogenous products. The condition is one in which the liver as a functioning organ suffers almost complete, if not complete, destruction, without similar apparent injury to other organs; and the failure in yellow atrophy of definite steps in nitrogenous metabolism may be taken as an indication of the possibility that such steps are normally achieved either by the liver or with its aid.

## REVIEW OF LITERATURE

Since Frerichs<sup>1</sup> (1861) established the presence of leucin and tyrosin in both the liver and urine in acute yellow atrophy, there has been basis for the belief that in this disease the liver proteins are digested to amino-acids, which are excreted as such in the urine. Schultzen and Reiss<sup>2</sup> (1869) are quoted as declaring that the presence of leucin and tyrosin in the urine indicates acute yellow atrophy as definitely as the presence of albumin indicates nephritis. In nearly all cases reported, however, the amino-acids have been identified only by microscopic examination of the crystals, and Rohmann<sup>3</sup> (1888) with the utmost care was unable definitely to identify either leucin or tyrosin in the antemortem urine in a case terminating fatally. Rohmann explained the failure of these substances to appear in some cases of yellow atrophy by the hypothesis that amino-acids are excreted only when formed at a rate faster than they can be destroyed in the body. In his case an aromatic acid, probably p-hydroxy-phenyl lactic acid, formed by replacing the NH<sub>2</sub> group of tyrosin by an OH (Ellinger and Kotake,<sup>4</sup> 1910), was obtained from the urine. Its presence indicated that the body could still deaminize tyrosin, even though the product of deamination failed of further combustion.

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\* From the Hospital of The Rockefeller Institute for Medical Research

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3 Rohmann. *Berlin klin. Wchnschr.* 861, 882, 1888

4 Ellinger and Kotake. *J. Biol. Chem.* 5: 129, 1903



Neuberg<sup>5</sup> (1909) claimed to have obtained from the blood serum in a fatal case tyrosin, leucin and lysin, the three amino-acids together amounting to about 6 gm per liter of blood. This indicated the presence of so great an amount of amino-acids in the blood, that the investigators believed they must be due to autolysis of the muscles as well as the liver. At the same time, the nitrogen distribution in the urine was normal, 76 per cent of the total nitrogen being in the form of urea. The results of the blood and urine analyses are both so unusual and so completely at variance with each other (i e, tremendous amounts of amino-acids in the blood with no apparent disturbance of the nitrogen distribution in the urine) that without confirmation their acceptance as accurate in a quantitative sense is difficult.

Wells<sup>6</sup> (1909) has published the most complete examination of the liver in yellow atrophy. He submitted the noncoagulable, water-soluble extract to Fischer's ester process for isolation of the mono amino-acids, and to Kossel's procedure for the diamino acids, and identified histidin, lysin, tyrosin, leucin, glycin, alanin, prolin, glutaminic acid and aspartic acid, the total amount being 8.67 gm from the entire liver. To judge from the usual losses by the ester method, the amounts present were probably twice as great as those actually obtained. Wells proved beyond doubt that the liver in acute yellow atrophy does contain considerable amounts of the various amino-acids yielded by proteins on hydrolysis. That previously only leucin and tyrosin were, as a rule, found was obviously due to the fact that these are the amino-acids which are most easily obtained by crystallization.

Even the results of Wells, however, did not entirely solve the problem from a quantitative standpoint. Van Slyke and Meyer<sup>7</sup> (1912), and Abel, Rowntree and Turner<sup>8</sup> (1914) showed that amino-acids in considerable amounts are *normal* constituents of the blood and tissues. The conceptions of the changes in liver atrophy, and their significance in regard to liver function, therefore, became dependent on the question whether or not the amounts of amino acids formed and excreted in acute yellow atrophy vary significantly from the normal. In the present paper we are able to answer this question in the affirmative, and thereby confirm the older conceptions of the metabolism in this disease and, we believe, place them on a more complete experimental basis.

#### REPORT OF CASE

The patient, female, aged 29 years, had been well to within one day of admission to the hospital. Her first symptoms were nausea and vomiting, at first mild, but persistent and gradually increasing in intensity. She had no chills, fever or pain. There was slight headache. Bowels were slightly constipated. The vomitus consisted of greenish, bile-tinged fluid.

On admission to the hospital, physical examination showed temperature was 100, pulse 75, respirations 20. Sclerae showed a very slight but definite icterus. Heart and lungs were negative. Abdomen negative. Liver and spleen not felt. Skin negative, no jaundice.

*Second day*—Patient continued vomiting all day, no pain. Temperature 99.6. Definite jaundice had developed over the entire body.

*Third day*—Vomiting persistent and intractable. She was unable to retain even water by mouth. Jaundice much more marked.

*Fourth day*—She was very weak and restless. No pain, no headache. All measures to allay the continuous vomiting were unsuccessful. Jaundice deeper. The abdomen, heart and lungs continued negative. Pulse 90, respirations 20, temperature 100.0 F.

5 Neuberg and Richter. *Deutsch med Wchnschr* 30 499, 1904.

6 Wells. *Arch Int Med* 9 628, 1907.

7 Van Slyke and Meyer. *J Biol Chem* 16 197, 1913.

8 Abel, Rowntree and Turner. *J Pharmacol Exper Therap* 5 275, 1914.

*Fifth day*—Patient vomited continually. Later she gradually sank into coma. No convulsions. Sclerae and skin of a deep greenish-yellow color. Pupils were widely dilated but equal, and reacted slightly to light. Fundi oculi showed nothing. Blood pressure, 155/70. Abdomen soft. Liver and spleen not felt. Liver dulness extended from fourth rib to just below the costal margin. All extremities quite rigid, no Kernig. Exaggerated knee jerks on both sides. Marked double ankle clonus. Definite Babinski on the left side, none on the right. No Chvostek or main d'accoucheur.

Lumbar puncture. No increased pressure. Fluid clear, cells 5 per c.c., spinal fluid urea nitrogen, 0.073 gm per liter. No bile (Smith's test).

In the late afternoon rigidity of the extremities and Babinski disappeared, and the knee jerks became less marked. No convulsions at any time or further evidence of tetany. No subcutaneous hemorrhages, at point of pressure, however, by the bed clothes there were small areas of ecchymosis. No diminution of the liver dulness made out during the day.

*Sixth day*—Patient continued comatose, temperature and pulse rapidly rising. At 8 a.m., temperature was 108, pulse, 145, respirations, 44. No decrease of liver dulness made out.

Patient died at 8:33 a.m.

Wassermann completely anticomplementary.

*Necropsy findings*—Macroscopic. Skin was deeply jaundiced, of a yellowish-green color. Lungs were normal, except for a few scattered, hemorrhagic patches. Heart was negative. Abdomen. Omentum and the mesentery showed everywhere numerous hemorrhagic areas from 3 to 5 cm. in diameter. Stomach and intestines, gallbladder, pancreas, kidneys, suprarenals and uterus were normal. Ovaries contained few cysts. Spleen not enlarged, extremely dark in color. On section it was quite soft. Cut surface was a very dark purplish red. Malpighian bodies were not well made out.

Liver was quite markedly diminished in size. It was not found fallen away from the anterior abdominal wall. Its upper border corresponded with the fourth rib, its lower border to the costal margin. Weight, 1,000 gm. Capsule was smooth, and the parenchyma shining through appeared quite yellowish. Liver substance was extremely friable and cut with great ease. On section, the liver surface showed at the center of each lobule a dark reddish area surrounded by a lighter yellow zone. This appearance was quite uniform throughout the entire liver, except that there were occasional patches from 5 to 10 mm. in diameter of a darker red, and these areas were sunken below the general surface. Other areas, larger in size, were yellowish and studded with small reddish points representing the centers of the lobules. In these yellowish patches the centers of the lobules were smaller and less numerous than in other parts of the liver. There were no areas which suggested adenomatous hyperplasia.

Microscopic. Only the liver and kidney appeared abnormal under the microscope. The uterus, spleen, suprarenals, pancreas, lungs and bladder were examined, with negative results.

Kidney. There are scattered throughout the cortex small areas of hemorrhage between the tubules and in Bowman's capsule. Glomeruli appear quite normal, but the tubules show here and there a moderate degree of fatty infiltration and cloudy swelling. Otherwise the parenchyma was normal.

Liver. Universally, the histologic picture is characterized by an extensive destruction. Throughout most of the liver, cells are represented by only faint outlines with completely or partially disintegrated nuclei. In some areas the liver cells are represented only by a structureless debris, while in others the outlines of the cell bodies can be faintly made out still in lobular arrangement. There is an extensive fatty infiltration. These changes involve practically all of the lobule, but are most extensive at the periphery. At the center of each lobule the bile duct epithelium is practically intact and here may be found quite generally very few liver cells in a better state of preservation. Some of the

bile ducts are surrounded by well preserved liver cells arranged in strands. Scattered throughout, mainly at the periphery of the lobules, are areas of blood extravasation.

*Analytical Methods*—Urine Analyses Chlorids were titrated by the Volhard method. Urea was determined by Van Slyke and Cullen's<sup>9</sup> (1917) modification of Marshall's urease method, using Squibb's urease prepared from Jack beans, ammonia by the aeration technic described by Van Slyke and Cullen. The total amino-acid nitrogen was determined as described by Levene and Van Slyke<sup>10</sup> (1912), the creatinin by Folin's<sup>11</sup> (1905) method, and the uric acid by Folin and Shaffer's<sup>12</sup> (1901) method. Total acetone bodies were estimated by Van Slyke's<sup>13</sup> (1917) gravimetric method. The titratable acid was determined according to Folin<sup>14</sup> (1903) by titration with phenolphthalein in the presence of potassium oxalate.

*Blood Analyses* The urea was determined as described by Van Slyke and Cullen<sup>15</sup> (1914), the amino-acid nitrogen by Van Slyke's nitrous acid method as described by Whipple and Van Slyke<sup>16</sup> (1918). The plasma bicarbonate was estimated by the carbon dioxide capacity method of Van Slyke and Cullen<sup>9</sup> (1917).

*Liver Analysis*—Water content Three samples of from 2 to 3 gm weight each from different lobes of the liver were dried in glass dishes at 110 C to constant weight. The results were 71.6, 71.6 and 71.9 per cent water.

*Total Nitrogen*—The dried samples used for water determination were Kjeldahlized. The results were 8.0, 8.36 and 9.0 per cent of nitrogen calculated on the dried samples, and 2.28, 2.34 and 2.51 per cent calculated on the fresh samples, an average of 2.38 per cent of the fresh substance, or 8.45 per cent of the dried. Using the approximate factor 6.25 for conversion of nitrogen figure into protein figure, this would indicate that 5.3 per cent of the dry substance was protein.

*Fat*—Three samples of from 6 to 12 gm from different lobes were let stand over night with 100 cc of 95 per cent alcohol each. The alcohol was poured off, the liver samples were minced, and were extracted with ether in a Soxhlet apparatus. The alcohol extracts were concentrated nearly to dryness, taken up with ether, and combined with the ether extracts. The latter were concentrated to dryness, and taken up with petroleum ether in weighed flasks. After the petroleum ether had been mostly removed on the water bath, the flasks were dried in an evacuated desiccator over sulfuric acid to constant weight. The results were 12.7, 13.8 and 14.0 per cent of fat, an average of 13.5 per cent of the fresh liver, or 47.7 per cent of the dry substance.

*Extraction of Nonprotein Nitrogen*—Three samples, totalling 303 gm, were cut with scissors into pieces which were dropped into 1.5 liters of boiling water slightly acidified with acetic acid. After the tissues were coagulated, the water was decanted, the pieces were minced, and the extraction with hot water was repeated three times. The decanted extracts were filtered through glass wool, then mixed with 50 gm kaolin, and filtered through paper with suction, the residue being washed with hot water. The clear amber filtrate was boiled down in an enamelled ware vessel to about 500 cc, and poured into three volumes of absolute alcohol to complete the removal of proteins. The next day the pre-

9 Van Slyke and Cullen. *J Biol Chem* **30** 289, 1917. Van Slyke, Stillman and Cullen. *J Biol Chem* **30** 401, 405, 1917.

10 Levene and Van Slyke. *J Biol Chem* **12** 301, 1912, **16** 125, 1913.

11 Folin. *Am J Physiol* **13** 48, 1905.

12 Folin and Shaffer. *Ztschr physiol Chem* **32** 552, 1901.

13 Van Slyke. *J Biol Chem* **32** 455, 495, 499, 1917.

14 Folin. *Am J Physiol* **9** 265, 1903.

15 Van Slyke and Cullen. *J Biol Chem* **19** 211, 1914.

16 Whipple and Van Slyke. *J Exper M* **28** 213, 1918.

precipitate which formed was filtered off, and washed with 80 per cent alcohol. The filtrate was concentrated under reduced pressure and brought to a volume of 150 cc.

*Free Amino Nitrogen*—Two c.c. portions of extract were used for the determination of amino nitrogen by the nitrous acid method of Van Slyke<sup>17</sup> (1912), the reaction being continued for 35 minutes at 22 C. The volume of gas yielded in three determinations was 9.55, 9.50 and 9.65 cc at 22 C, 761 mm, the average, 9.57 cc, indicating 540 mg of amino nitrogen, or 134 mg per 100 gm of fresh liver.

*Peptid Nitrogen*—Five c.c. samples of the extract were mixed in test tubes with 5 c.c. portions of concentrated hydrochloric acid and heated for twenty-four hours at 100 C. The hydrochloric acid driven off on the water bath, and the residue diluted to 20 cc, of which 2 c.c. portions were used for the amino nitrogen determination. The determinations yielded 3.72, 3.67 and 3.63, average 3.67 cc of nitrogen at 22 C, 759 mm, indicating 206 mg of amino nitrogen per 100 gm of fresh tissue. Subtracting the 134 mg present as per amino nitrogen before hydrolysis, leaves 72 mg as peptid nitrogen, freed by hydrolysis.

*Urea and Ammonia Nitrogen*—These determinations were made as in urine (Van Slyke and Cullen,<sup>9</sup> 1914), 5 c.c. of extract being used for urea and the same amount for ammonia. The results of triplicate determinations indicated 148 mg of urea nitrogen and 34.5 mg of ammonia nitrogen per 100 gm of fresh tissue.

*Creatinin*—Folin's method was used as for urine<sup>11</sup> (1905), except that the final dilution was less. Five c.c. of the extract were mixed with 15 c.c. of saturated picric acid solution, and 5 c.c. of 10 per cent sodium hydroxide. At the end of five minutes the solution was diluted to 50 cc and read against a dichromate standard. The result, which may be somewhat high because of the relative concentration of sodium picrate, indicated 3.3 mg of creatinin nitrogen per 100 gm of fresh tissue.

*Creatin Plus Creatinin*—Five c.c. of extract were heated at 100 C with 5 c.c. of N hydrochloric acid for three hours. The hydrochloric acid was neutralized with concentrated sodium hydroxide, and 5 c.c. of 10 per cent sodium hydroxide in excess were added with 15 c.c. of saturated picric acid. After five minutes the solution was diluted to 100 cc and read against a chromate standard. The reading indicated 17.6 mg of creatin plus creatinin nitrogen, or 14.3 mg of creatin nitrogen per 100 gm of fresh liver tissue.

The technic used is similar to that employed by Janney and Blatherwick<sup>18</sup> (1915). The difference is that the above authors used aluminum hydroxide to adsorb uncoagulated protein (presumably gelatin), while we used kaolin. Creatinin under proper conditions is adsorbed by kaolin (Greenwald,<sup>19</sup> 1918), but we found by control tests that the kaolin preparation used by us in the amounts employed did not remove sufficient creatinin to significantly affect results such as were obtained.

#### DISCUSSION OF RESULTS

*Excretion*—The comatose condition of the patient made collection of complete twenty-four hour specimens impossible, so that conclusions have to be drawn largely on the nitrogen distribution. The abnormalities in the latter during the last two days before death are the

17 Van Slyke J Biol Chem, 1912

18 Janney and Blatherwick J Biol Chem 21 567, 1915

19 Greenwald J Biol Chem 34-103, 1918

high ammonia ratio, and even more strikingly, the high amino acid nitrogen and the low proportion of urea nitrogen (Table 1) All three are explainable on the assumption that the liver had lost a part of its ability to transform amino-acid nitrogen into urea nitrogen, one portion being excreted in the form of unchanged amino-acids, and another in the form of ammonia

TABLE 1—SALT AND NITROGEN EXCRETION

Date, 1919	Output, O c †	Specific Gravity	Bile	NaCl, Gm per L	Total N, Gm per L	Urea N		Amino-Acid N		NH <sub>3</sub> N		Creatinin N		Uric Acid N		Undetermined N	
						Gm per L	Per Cent of Total N	Gm per L	Per Cent of Total N	Gm per L	Per Cent of Total N	Gm per L	Per Cent of Total N	Gm per L	Per Cent of Total N	Gm per L	Per Cent of Total N
Feb 28	1,070	1 013	+			3 11				0 392							
Mar 1	250+	1 022	++	1 04	13 90	7 04	47 2	0 61	4 1	0 862	16 2	0 65	4 4	0 185	1 2	4 65	32 7
Mar 2	411+	1 032	++	0 25	10 94	5 68	51 9	1 75	16 0	1 880	17 2	0 54	2 0	0 123	1 7	0 96	8 1
Mar 3	130+	1 031	+	1 38	16 64	7 75	46 6	2 22	13 3	1 925	11 6	0 49	2 9	0 417	2 5	3 82	23 0

\* Tyrosin crystals were obtained from the combined specimens of urine not used for other analyses  
 † Part of urine was lost on March 1, 2 and 3 because of patient's comatose condition

The amount of nitrogen eliminated cannot be stated accurately because of the lack of twenty-four hour samples of urine The probable minimum can, however, be approximately estimated from the creatinin The creatinin nitrogen excretion of an individual of the patient's size (about 50 kg) would normally be about 4 40 gm The twenty-four hour excretions of nitrogen and of ammonia plus titratable acid, estimated in this manner, are given in Table 2 In an acute illness

TABLE 2—APPROXIMATE TWENTY-FOUR HOUR NITROGEN AND ACID EXCRETIONS ESTIMATED FROM CREATININ OUTPUT

Date	A Creatinin N per L	B Proportion of 24 Hr Excretion in 1 Liter of Urine Sample Obtained Estimated from Creatinin, A	Estimated Excretion per 24 Hours = Excretion per Liter Urine	
			B	
	Mg	400	Titratable Acid + NH <sub>3</sub> , O c 0 1 N	Total N, Gm
March 1	650	1 62	670	8 6
March 2	540	1 35	1,530	8 1
March 3	490	1 22	1,530	13 6

with pathologic tissue loss, the creatinin output might be increased Even if it remained only normal at 0 40 gm per day, however, the total nitrogen excretion on March 1, 2 and 3 would be calculated at 8 6, 8 1 and 13 6 gm, respectively, assuming that the ratio of twenty-four hour total nitrogen to the observed nitrogen per liter is as 0 40 to the observed creatinin nitrogen per liter The first two figures

might be considered normal for a fasting individual (Lusk<sup>20</sup> 1917) but the last is certainly high and corresponds with the incidence of fever.

Small amounts of acetone bodies were excreted but in quantities not sufficient to be of significance for the acid-base balance of the body.

The low salt output was presumably due to lack of salt intake rather than kidney retention.

TABLE 3—ACID EXCRETION AND ALKALINE RESERVE

Date 1919	Excretion per Liter of Urine			Total Acetone Bodies Cc 0.1 N	Blood Plasma Bicarbonate CO <sub>2</sub> Volume per Cent
	NH <sub>3</sub> , Cc 0.1 N	Titratable Acid Cc 0.1 N	Acid—NH <sub>3</sub> Cc 0.1 N		
February 28.	289	92.4	372		
March 1	615	479	1096	64	
March 2	1340	719	2059	189	95.5
March 3	1375	476	1851		65.4
March 4					49.0

*Blood Analyses.*—The analyses of the blood like those of the urine, indicate a loss of diamnifying function in the body (Table 4). The amino nitrogen contents on the last two days are respectively two and three times as great as the 7 to 8 mg per 100 cc which represent the average normal (Bock<sup>21</sup> 1917). The apparent explanation is that the liver had lost the ability to transform amino-acids into urea, an ability which has been demonstrated in the normal liver by the perfusion experiments of Salaskin<sup>22</sup> (1898) recently confirmed by Jansen (1915) and by the physiological experiments of Van Slyke, Meyer, Cullen and McLean (Van Slyke,<sup>23</sup> 1917).

TABLE 4—UREA AND AMINO-ACID NITROGEN IN THE BLOOD

Date, 1919	Urea N, Gm per L	Amino-Acid N, Gm per L
February 28	—	—
March 1	—	—
March 2	0.123	0.140
March 3	0.088	0.173
March 4	0.159	0.283

The source of the amino-acids in the blood in our case was undoubtedly autolyzed tissue protein. The patient because of the nausea, retained practically no food; the considerable amounts of nitrogen excreted (8 gm or more per day) must have come from tissues autolyzed under the influence of the fasting and intoxication attending the disease.

20 Lusk. Science of Nutrition Philadelphia 1917

21 Bock, J. C. J. Biol. Chem. 29:191, 1917

22 Salaskin. Ztschr. f. physiol. Chem. 25:128, 1898

23 Van Slyke. Arch. Int. Med. 19:55 (Jan.) 1917

The blood urea remains within normal limits. Taken with the continued output of urea in the urine, it shows that the urea-forming function of the body, although diminished, was only partially lost, even on the day before death.

The blood plasma bicarbonate determinations (Table 3) gave a peculiar result on the first observation four days before death. The carbon dioxide capacity of 96.5 per cent would indicate an abnormally high alkaline reserve. Unfortunately, the observation was not repeated on that day, and we are uncertain whether an increased blood bicarbonate actually existed, or whether there was an error in the determination. The carbon dioxide estimations were done in duplicate, but the carbon dioxide capacity might have been raised *in vitro* by contamination of the centrifuge tube or equilibrating funnel with alkali. That this may have occurred is made more probable by the fact that the excretion of titratable acid and ammonia on this day was above the usual normal limits.

On the last two days before death, there was a high excretion of titratable acid and ammonia, about double the normal, and on the day before death the plasma bicarbonate fell slightly below normal (49 per cent of carbon dioxide). These facts indicate a definitely accelerated formation of acids in the organism, but neither the acid excretion nor the plasma bicarbonate indicates an acidosis sufficient to have in itself a definite effect on the patient's condition. (Compare Van Slyke,<sup>24</sup> 1917 [b]). In connection with the increased acid production it is of interest to note that Rohmann<sup>3</sup> (1888) obtained unusual aromatic acids and considerable amounts of sarcolactic acid from the urine in a case of yellow atrophy.

*Composition of the Liver*—The most striking change in the liver was the marked loss of substance, which is usually noted in acute atrophy (Wells,<sup>6</sup> 1907). The liver weighed only 1,000 gm. instead of the 1,800 gm., which, for an individual of the patient's size, is normal, according to Frerichs<sup>1</sup> (1861).

The water content of 71.7 per cent (Table 5) shows no increase over that of the normal liver analyzed by Wells, in fact is less than the latter (76.1 per cent). In this respect this case differs from most of those in the literature, as the water content usually has been found high in acute yellow atrophy.

The fat content of 13.5 per cent is decidedly high, the normal being quoted by Wells<sup>6</sup> (1907) as about 3 per cent. The livers of acute atrophy of which analyses are reported in the literature (Wells, 1907, 1908) have been found to vary between from 2.0 and 8.7 per cent in fat content, while those of phosphorus poisoning and fatty degenera-

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<sup>24</sup> Van Slyke. J. Biol. Chem. **32** (b)455 1917.

tion show from 25 to 30 per cent. In our case of acute atrophy the difference from the high fat values of phosphorus poisoning and fatty degeneration is much less striking than in any of the instances reported. It may be that the unusually rapid progress, with death a few days after the first symptom, prevented the complete combustion of the fat transported to or formed in the liver. The high fat content in our case is the cause of the normally high content of total solids noted in the preceding paragraph, fat increase makes up for the protein loss.

TABLE 5—DRY MATTER, FAT AND TOTAL NITROGEN IN LIVER

	Per Cent	Normal Values, per Cent *	
Water	71.7	77.6	76.1
Dry matter	28.3	19.4	20.9
Dry matter as fat	13.5	5.0	3.0
Dry matter as protein calculated as $N \times 6.25$	14.9	28.4	

\* From Wells (1903)

TABLE 6—NITROGEN DISTRIBUTION IN LIVER

	Per 100 Grams Liver, Gm	Proportion of Total N, per Cent
<b>A Total N</b>		
Total N	2.350	100.0
Nonprotein N	0.315	13.2
Protein N (by difference)	2.035	86.8
<b>B Nonprotein N</b>	Per 100 Grams Fresh Liver, Gm	Proportion of Total Nonprotein N, per Cent
Total nonprotein N	0.3130	100.0
Urea N	0.0148	4.76
Ammonia N	0.0345	10.95
Amino N	0.1340	42.50
Peptid bound N	0.0720	22.80
Creatin N	0.0143	4.54
Creatinin N	0.0033	1.05
Undetermined N	0.0421	13.40

The "dry matter not fat," which, as indicated by its nitrogen content, was nearly all protein, was much decreased, as it has been in all the reported cases of liver atrophy, whether due to poisoning or to acute disease. In our case the content of solids not fat, or approximately the protein, is 14.9 per cent instead of the normal 20 per cent of fresh liver. During the few days of the disease, the liver, therefore, in losing about 45 per cent of its weight lost about 60 per cent of the protein substance.

In the nitrogen distribution in the liver (Table 6) the main point of interest is the high content of amino-acid and peptid nitrogen. Compared with livers of normal dogs, the amino nitrogen, 0.134 per



cent of the fresh tissue, is about three times as great (Van Slyke and Meyer,<sup>7</sup> 1913) The observed amino nitrogen content indicates the presence of approximately 13 or 14 gm of free amino-acids in the 1,000 gm of liver tissue

#### RÔLE OF THE LIVER IN NITROGENOUS METABOLISM

The apparent significance of these figures, along with those for the blood and urine, is that the liver protein was autolyzed at a rapid rate to amino-acids and peptids, chiefly the former, and that amino-acids produced by the abnormal autolysis of the liver and the normal autolysis of the rest of the body (other organs were not macroscopically or microscopically degenerated) were turned into urea to the extent of only about 60 per cent instead of from 85 to 95 per cent The excreted amino-acids formed as high as 16 per cent of the total urinary nitrogen instead of the normal 2 per cent

There was no indication at any time of a tendency for the urea nitrogen output to fall much below 50 per cent of the total nitrogen In view of the apparently complete degeneration of the liver cells the data consequently suggest the probability that, although deamination and urea synthesis without the liver are incomplete, nevertheless they can occur to such an extent that the greater part of the nitrogen normally excreted as urea is still in this form Fiske and Sumner<sup>25</sup> (1914) found that dogs could form urea from injected glycocoll even after the abdominal viscera had been excluded from the circulation It is uncertain whether a considerable part of the total urea synthesis normally occurs in parts other than the liver, or whether the process is taken up elsewhere only when the liver fails

It appears that acute yellow atrophy, with the possible exception of fatal phosphorus poisoning, is the only clinical condition in which unusual amounts of amino-acids have been demonstrated to be formed and excreted as such, without change to urea or ammonia

The most rapid autolysis unaccompanied by liver degeneration does not apparently result in the excretion of amino-acids For example, we have not found the amino nitrogen of the blood or urine increased during resolution in pneumonia, although this process represents one of the most striking examples known of rapid autolysis *in vivo* Nor was any abnormal increase in the blood amino nitrogen observed by Whipple and Van Slyke<sup>16</sup> (1918) in dogs that were intoxicated by proteose or by intestinal obstruction in such a manner that the blood urea was raised by autolysis of body protein in a few hours to form two to five times the fasting level Such urea changes indicate an amount of tissue digestion seldom met in disease, and not approximated in the apparently localized autolysis of yellow atrophy

25 Fiske and Sumner J Biol Chem 18 285, 1914

In order that amino-acids in exceptional amounts shall escape deamination and appear in abnormal amounts in the urine, it appears necessary not only that the liver shall be injured, but that its loss of function shall be profound, and, as stated above, such loss of function apparently has been observed in man with certainty only in acute atrophy. We have been unable to confirm the statement of Labbé and Bith<sup>26</sup> (1911) that it occurs in diabetes (Van Slyke and Stillman, unpublished results). It does not occur in the toxemias of pregnancy, despite the marked degenerative changes that occur in the liver (Losee and Van Slyke,<sup>27</sup> 1917). Levene and Van Slyke<sup>10</sup> (1912) failed to observe it in two cases of cirrhosis. Chesney, Marshall, and Rowntree<sup>28</sup> (1914) report somewhat increased amino-acid nitrogen in both blood and urine in more than 50 per cent of a series of cases with apparent liver insufficiency from various causes. However, the upper limits for amino nitrogen which they assumed were so low (1.5 per cent of the urine nitrogen, and 3 mg per 100 c.c. of blood) that they are readily exceeded in normal individuals (Levene and Van Slyke,<sup>10</sup> 1912, 1913, Bock,<sup>21</sup> 1917, Cullen, Ellis and Van Slyke,<sup>29</sup> 1915). The only case in their series with definitely high blood amino nitrogen was one of arsphenamin poisoning, with 12.4 mg per 100 c.c.

In pathologic liver conditions caused experimentally, it appears to be likewise unusual, unless liver degeneration is almost complete, to find increased amino acid content in blood or urine. Whipple and Van Slyke<sup>16</sup> (1918) failed to observe it in the blood of dogs with Eck fistulas (unpublished results). Levene and Van Slyke<sup>10</sup> (1912) did not find it in the urines of dogs in which Opie and Dochez had caused liver degeneration by phosphorus and chloroform poisoning. Only Marshall and Rowntree<sup>30</sup> (1915) observed an increase in the blood amino nitrogen (up to 21 mg per 100 c.c.) shortly before death in dogs poisoned with phosphorus.

In pathologic conditions not involving the liver, Bock<sup>21</sup> (1917) found very markedly increased blood amino nitrogen only in some cases of nephritis, in which amino acids are retained along with other urinary constituents.

#### SUMMARY

An increased excretion of ammonia and titratable acids was observed in the last days of illness, and a fall of plasma bicarbonate to slightly below normal on the day before death. Even at this time, however, the deviations from the normal were too small to indicate that acid intoxication was a significant factor in the condition.

26 Labbé and Bith. *Progres méd* 27 581, 1911.

27 Losee and Van Slyke. *Am J Med Sc* 153 94, 1917.

28 Chesney, Marshall and Rowntree. *J A M A* 63 1533, 1914.

29 Cullen, Ellis and Van Slyke. *J A M A* 64 126, 1915.

30 Marshall and Rowntree. *J Exper M* 22 333, 1915.

The results afford confirmation of a quantitative character for the belief that amino-acids are formed by autolysis in the atrophying liver, and circulate and are excreted as such in unusual amounts

The excretion of amino-acids did not appear to be due to increase in their rate of formation, for the total protein katabolism was not abnormally or even unusually rapid. The excretion appeared due rather to loss of power to deaminate amino-acids at even an ordinary rate

A review of the known instances of rapid *intra vitam* autolyses not involving the liver indicates that tissue waste alone does not cause increase of amino acids in the blood and urine. In conditions of less profound liver injury (eclampsia) a marked decrease may occur in the proportion of urinary nitrogen present as urea and ammonia, which are partly replaced by as yet unidentified nitrogenous substances (undetermined nitrogen), but excretion of definitely abnormal amounts of amino acids appears to result only when the destruction of the liver cells is almost complete

These observations support the view that in the deamination of amino acids and the synthesis of urea the liver bears a part which cannot be entirely assumed by the rest of the body

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